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CLINICAL RESEARCH

Frequent drinking is a more important risk factor for new-onset atrial fibrillation than binge drinking: a nationwide population-based study

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Aims Heavy consumption of alcohol is a known risk factor for new-onset atrial fibrillation (AF). We aimed to evaluate the relative importance of frequent drinking vs. binge drinking.

Methods and results A total of 9 776 956 patients without AF who participated in a national health check-up programme were included in the analysis. The influence of drinking frequency (day per week), alcohol consumption per drinking session (grams per session), and alcohol consumption per week were studied. Compared with patients who drink twice per week (reference group), patients who drink once per week showed the lowest risk [hazard ratio (HR) 0.933, 95% confidence interval (CI) 0.916–0.950] and those who drink everyday had the highest risk for new-onset AF (HR 1.412, 95% CI 1.373–1.453), respectively. However, the amount of alcohol intake per drinking session did not present any clear association with new-onset AF. Regardless of whether weekly alcohol intake exceeded 210 g, the frequency of drinking was significantly associated with the risk of new-onset AF. In contrast, when patients were stratified by weekly alcohol intake (210 g per week), those who drink large amounts of alcohol per drinking session showed a lower risk of new-onset AF.

Conclusion Frequent drinking and amount of alcohol consumption per week were significant risk factors for new-onset AF, whereas the amount of alcohol consumed per each drinking session was not an independent risk factor. Avoiding the habit of consuming a low but frequent amount of alcohol might therefore be important to prevent AF.

Keywords Atrial fibrillation • Alcohol • Drinking • Upstream therapy

Introduction

Atrial fibrillation (AF) is the most frequent tachyarrhythmia, and its consequences are not limited to symptoms but also extend to deleterious cardiovascular events, including ischaemic stroke.[1,2] The global medical burden of AF is estimated to rise rapidly due to increasing incidence of AF, largely attributable to the ageing of the general population.[3] Enormous work has been done to date to eliminate AF mainly through catheter ablation, direct current cardioversion, or use of antiarrhythmic drugs, but primary prevention of AF has not received enough attention.[4] Previous studies identified several risk factors for AF such as age, male sex, hypertension, diabetes mellitus, obesity, sleep apnoea, heart failure, and systemic inflammatory disease.[2,5,6] Alcohol consumption, especially to heavy degrees, is associated with an increased risk for new-onset AF.[7,8] However, the underlying mechanism of such an association is not clear. Alcohol is

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What's new?

- Weekly alcohol intake which is calculated by (drinking session per week) * (amount of alcohol consumed per drinking session) is a significant risk factor for new-onset atrial fibrillation (AF).
- According to our analysis, drinking session per week was the strongest risk factor for new-onset AF.
- However, consuming large amount of alcohol per drinking session, which is often called as binge drinking, was not associated with new-onset AF.
- Drinking small amount of alcohol frequently may not be a good strategy to prevent new-onset AF.

an established direct cardiotoxin but can render the atrial myocardium more susceptible to AF.[9,10] A substantial proportion of patients suffer from paroxysmal AF events after alcohol consumption, and previous research suggests alcohol consumption might trigger AF.[11]

A prior meta-analysis has demonstrated that the risk of new-onset AF had a linear correlation with the amount of alcohol.[8] Specifically, the risk of new-onset AF increased by 8% for every 12 g of alcohol consumed per week.[8] However, it is not clear which is more important: the total amount of alcohol or the number of drinking sessions. Repetitive drinking such as drinking every day can expose the patient to multiple triggered paroxysmal AF events that in turn can accelerate the progression of AF. Many physicians recommend their AF patients avoid binge drinking (the consumption of a large amount of alcohol in a single drinking session) and instead drink a divided dose of alcohol per day. However, the impact of frequent drinking is not clearly established and might be more dangerous than binge drinking. We performed this study to evaluate whether the number of drinks per week is more important than the absolute amount of alcohol intake per week in terms of new-onset AF.

Methods

Patients

The Korean National Health Insurance Service (K-NHIS) database was used for this study. Almost all Koreans (97.1%) are mandatory subscribers to the K-NHIS, a single medical insurer in the Republic of Korea that is managed by the government. Therefore, the K-NHIS database can feasibly be argued to represent the nature of the entire population of South Korea. This database contains baseline demographics, diagnosis codes of various diseases, use of inpatient and outpatient services, pharmacy dispensing claims, and mortality data. Furthermore, the K-NHIS offers a regular national health check-up for all subscribers and includes the following: a health questionnaire including alcohol consumption; laboratory tests such as lipid profile, serum creatinine, and fasting blood sugar; chest X-ray; and measurements of blood pressure, body weight, height, and waist circumference. The database is open for use by medical researchers if the study protocols are approved by the official review committee (https://nhiss.nhis.or.kr/).

The current study included patients who underwent a national health check-up in 2009. The screening period was from January 2002 to December 2008. The follow-up period was from the date of national health check-up to the date of diagnosis of new-onset or December 2017 if no new-onset AF was detected. Patients were excluded if they had already been diagnosed with AF during the screening period, had missing data regarding alcohol consumption, or if they were younger than 20 years old. For this study, we obtained the health questionnaire data regarding alcohol consumption. Since diagnostic codes related to AF were also retrieved, we were able to analyse the association between alcohol consumption pattern and risk of new-onset AF using a large number of patients with a sufficient follow-up duration.

Definitions

The diagnosis of AF required two outpatient records or one inpatient record of International Classification of Disease, 10th revision codes in the NHIS database. The robustness of this definition has been validated in previous studies.[12] The exact diagnostic codes for AF and other diseases are described in Supplementary material online, *Table S1*. The incidence of new-onset AF was defined as the number of newly diagnosed AF cases per 1000 patient-years of follow-up. Smoking status was defined as follows: (i) current-smokers were those who had smoked at least 100 cigarettes in their lifetime and who continued smoking within 1 month of their 2009 national health check-up; (ii) ex-smokers were those who smoked at least 100 cigarettes in their lifetime but who did not smoke within 1 month of their 2009 national health check-up; and (iii) never-smokers were those who had smoked less than 100 cigarettes in their lifetime.

Alcohol intake

From the questionnaire provided as part of the national health check-up, two parameters were obtained as follows: (i) number of days a given person drinks and (ii) amount of standard drinks (cups) per each drinking session. A standard drink was defined as a specialized cup for each type of alcohol such as beer, Korean traditional alcohol (soju), or whisky. Each cup has a different volume but is able to hold a similar amount of alcohol (8 g). The exact methods to calculate the amount of alcohol consumed per each standard drink is described in Supplementary material online, *Methods*. The total amounts of alcohol intake per week and each drinking session, respectively, were calculated. Based on the total amount of alcohol intake per week, patients were classified as follows: (i) non-drinker: 0 g of alcohol per week; (ii) mild drinker: less than 105 g but more than 0 g of alcohol per week; (iii) moderate drinker: 105 g or more but less than 210 of alcohol per week; and (iv) heavy drinker: 210 g or more of alcohol per week.

Study endpoints

The occurrence of new-onset AF was the endpoint of this study. The incidence of new-onset AF was defined as the number of new-onset AF cases calculated for 1000 patient-years of follow-up. The risk of new-onset AF was stratified by alcohol consumption pattern. The impacts of both absolute alcohol intake and number of drinks per week were evaluated.

Statistical analysis

A Student's *t*-test was used to compare continuous variables, which were described as the mean ± standard deviation. Categorical variables are presented as percentile values and were compared using a χ^2 test. Univariate and multivariate Cox regression analyses were performed to calculate the hazard ratio (HR) and 95% confidence interval (CI) of each independent variable. Multivariate Model 1 was adjusted for age and sex, while Model 2 was adjusted for age, sex, smoking status, physical activity, income level, diabetes, hypertension, and dyslipidaemia. All significance tests were two-tailed, and *P*-values of 0.05 or less were considered to be

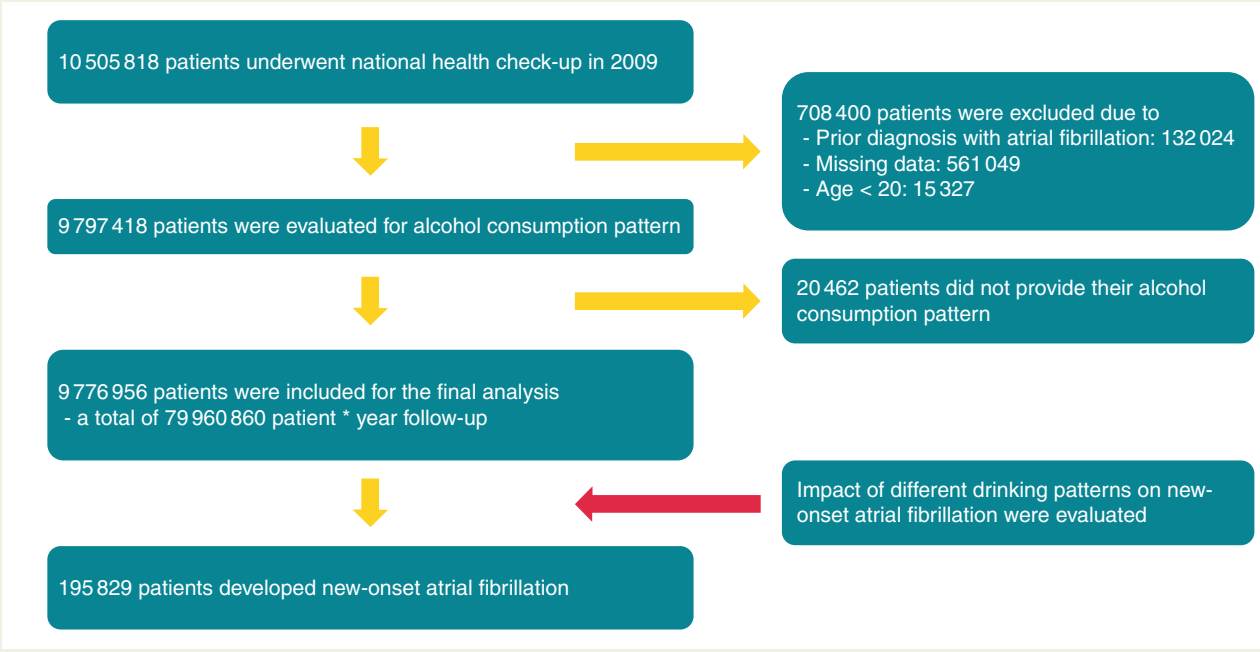

Figure 1 Flowchart of the study.

statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

A total of 9 776 956 patients were included in the analysis. A flowchart of the study population enrolment is presented in *Figure 1*. According to the study definition, 51.3%, 32.1%, 9.7%, and 6.9% of patients were classified as non-drinkers, mild drinkers, moderate drinkers, and heavy drinkers, respectively. Non-drinkers were older, more often female, had a lower prevalence of a smoking history, were shorter, had lower body weights, had smaller waist circumferences, and had lower blood pressures. The baseline characteristics of the study population are summarized in *Table 1*.

Weekly intake of alcohol and new-onset atrial fibrillation

Incidences of new-onset AF were 2.84, 1.85, 2.21, and 2.67 for non-drinkers, mild drinkers, moderate drinkers, and heavy drinkers, respectively. In multivariate analysis, mild drinkers had the lowest risk for new-onset AF and so were set as a reference population. Non-drinkers and moderate drinkers had 8.6% (HR 1.086, 95% CI 1.073–1.099; *Table 2*) and 7.7% (HR 1.077, 95% CI 1.059–1.097; *Table 2*) increased risks of developing new-onset AF, respectively. Heavy drinkers showed the highest risk for new-onset AF with a 21.5% (HR 1.215, 95% CI 1.193–1.238; *Table 2*) increased risk compared with mild drinkers. When weekly alcohol intake was set as a continuous variable (as a gram), there was a 2% increase in the risk of new-onset AF per each gram of alcohol consumed per week (Supplementary material online, *Table S2*).

The relationship between weekly alcohol intake and new-onset AF was evaluated in subgroup analysis stratified by sex and age (*Table 3*). Although the overall incidence and HR differed significantly according to sex and age, the influence of weekly alcohol intake was still significantly associated with the risk of new-onset AF in each subgroup (*Table 3*).

Frequent drinking and new-onset atrial fibrillation

The number of drinking sessions per week was significantly associated with the development of new-onset AF (*Table 2*). In comparison with patients who drink twice per week (reference group), patients who drink once per week showed the lowest risk (HR 0.933, 95% CI 0.916–0.950; *Table 2*) and patients who drink everyday had the highest risk (HR 1.412, 95% CI 1.373–1.453; *Table 2*), respectively, for new-onset AF. Additionally, the risk of new-onset AF was higher in patients who do not drink vs. those who drink once or twice per week (*Table 2*). The number of drinking sessions was associated with the risk of new-onset AF regardless of age and sex (*Table 4*). Although weekly alcohol intake was associated with the risk of new-onset AF, such association was lost when drinking frequency was included in the multivariate model (Supplementary material online, *Table S2*).

Amount of alcohol intake per drinking session

There was a significant inverse relationship between the amount of alcohol consumed per drinking session and the risk of new-onset AF,

Table 1 Baseline demographics

	Weekly alcohol intake				
	Non-drinker (0 g) (n = 5 016 718)	Mild drinker (0 ≤ g < 105) (n = 3 136 554)	Moderate drinker (105 ≤ g < 210) (n = 950 963)	Heavy drinker (≥210 g) (n = 672 721)	*P*-value
Sex					<0.001
Male	1 707 780 (34.04%)	2 148 445 (68.50%)	854 406 (89.85%)	632 545 (94.03%)	
Female	3 308 938 (65.96%)	988 109 (31.50%)	96 557 (10.15%)	40 176 (5.97%)	
Smoking history					<0.001
Non-smoker	4 008 984 (79.91%)	1 485 122 (47.35%)	211 783 (22.27%)	116 443 (17.31%)	
Ex-smoker	415 693 (8.29%)	589 739 (18.80%)	224 922 (23.65%)	159 845 (23.76%)	
Current smoker	592 041 (11.80%)	1 061 693 (33.85%)	514 258 (54.08%)	396 433 (58.93%)	
Regular exercise	2 166 864 (43.19%)	1 893 489 (60.37%)	572 720 (60.23%)	376 738 (56.00%)	<0.001
Low income (lower quartile)	1 458 369 (29.07%)	775 675 (24.73%)	205 076 (21.57%)	147 971 (22.00%)	<0.001
Hypertension	1 380 458 (27.52%)	645 344 (20.57%)	253 950 (26.70%)	202 789 (30.14%)	<0.001
Dyslipidaemia	1 045 415 (20.84%)	453 088 (14.45%)	155 435 (16.35%)	116 790 (17.36%)	<0.001
Diabetes mellitus	477 144 (9.51%)	207 613 (6.62%)	83 875 (8.82%)	72 867 (10.83%)	<0.001
Age (years)	50.65 ± 14.28	42.89 ± 12.89	43.52 ± 12.32	44.29 ± 12.68	<0.001
Height (cm)	160.30 ± 8.81	166.65 ± 8.34	169.39 ± 7.16	169.99 ± 6.90	<0.001
Weight (kg)	60.77 ± 10.71	65.74 ± 11.50	69.50 ± 11.03	70.75 ± 11.28	<0.001
Body mass index (kg/m^2)	23.59 ± 3.25	23.58 ± 3.15	24.16 ± 3.09	24.42 ± 3.17	<0.001
Waist circumference (cm)	79.10 ± 9.10	80.20 ± 9.00	83.05 ± 8.22	84.15 ± 8.21	<0.001
Systolic blood pressure (mmHg)	121.72 ± 15.37	121.65 ± 14.27	125.24 ± 14.23	126.75 ± 14.51	<0.001
Diastolic blood pressure (mmHg)	75.41 ± 9.95	76.22 ± 9.79	78.72 ± 9.80	79.64 ± 9.94	<0.001
Fasting glucose (mg/dL)	96.82 ± 22.84	95.93 ± 21.26	99.11 ± 24.26	101.45 ± 27.03	<0.001
High-density lipoprotein (mg/dL)	55.19 ± 20.45	55.57 ± 16.89	55.55 ± 16.91	56.37 ± 17.92	<0.001
Total cholesterol (mg/dL)	196.15 ± 37.35	192.95 ± 35.42	195.70 ± 35.96	196.12 ± 36.74	<0.001
Triglyceride (mg/dL)	107.53 (107.47–107.58)	111.45 (111.38–111.52)	134.69 (134.52–134.85)	146.39 (146.18–146.61)	<0.001
CHA_2DS_2-VASc	1.334 ± 1.245	0.631 ± 0.873	0.437 ± 0.811	0.443 ± 0.836	<0.001

with low amounts of alcohol consumed per session associated with an increased risk of new-onset AF (*Table 2* and *Figure 2*). Those who drink 32–56 g of alcohol per drinking session were used as a reference. Non-drinkers showed a higher risk of new-onset AF, and the risk decreased as alcohol intake per drinking session increased. However, there was a slight increase in the risk of new-onset AF in those who drink more than 112 g of alcohol per drinking session compared with the reference group (*Table 2* and *Figure 2*). The inverse relationship was maintained when amount of alcohol consumed per drinking session was included in the multivariate model as a continuous variable (Supplementary material online, *Table S2*).

Adjusted HRs of new-onset AF for each drinking pattern are summarized in *Figure 2*. The weekly intake of alcohol and frequency of drinking was associated with the development of new-onset AF. However, the amount of alcohol consumption per drinking session did not show any clear association with new-onset AF. Regardless of whether weekly alcohol intake exceeded 210 g, the frequency of drinking was significantly associated with risk of new-onset AF (*Table 5*). If drinking frequency was equal, incidence and adjusted HR for new-onset AF were similar between those who drink more than and less than 210 g per week (*Table 5*). In contrast, when patients were stratified by weekly alcohol intake (210 g per week), those who drink large amounts of alcohol per drinking session showed a lower risk of new-onset AF (*Table 5*).

Discussion

The current study revealed that (i) weekly alcohol intake was significantly associated with risk of new-onset AF, where mild drinkers and heavy drinkers had the lowest and highest risks for new-onset AF, respectively; (ii) the amount of alcohol intake per drinking session was inversely associated with the risk of new-onset AF; and (iii) the frequency of drinking was significantly associated with the risk of new-onset AF. Weekly alcohol intake is defined as the frequency of drinking per week multiplied by the amount of alcohol intake per drinking session, and according to our analysis, it is the frequency of drinking (not the amount of alcohol intake per drinking session) that determines the increased risk of new-onset AF. By considering national health check-up data, this study reports on the impact of frequent drinking vs. binge drinking on new-onset AF with the largest sample size to date. Given that we were able to include a sufficient number of patients in this study, we were able to perform various subgroup analyses, such as those based on sex, age, and weekly alcohol intake.

Table 2 Risk of new-onset atrial fibrillation according to drinking status

	N	Event number	Patient* year	Incidence	Multivariate Model 1 (HR)	Multivariate Model 2 (HR)	Multivariate Model 3 (HR)
Weekly alcohol intake (g)							
Non-drinker (0 g)	5 016 718	116 123	40 915 000	2.838	1.134 (1.121–1.148)	1.086 (1.073–1.099)	1.069 (1.056–1.082)
Mild drinker (0 ≤ g < 105)	3 136 554	47 729	25 786 282	1.851	1 (reference)	1 (reference)	1 (reference)
Moderate drinker (105 ≤ g < 210)	950 963	17 224	7 784 544	2.213	1.116 (1.097–1.136)	1.077 (1.059–1.097)	1.089 (1.070–1.108)
Heavy drinker (≥ 210 g)	672 721	14 753	5 475 034	2.695	1.288 (1.264–1.312)	1.215 (1.193–1.238)	1.232 (1.209–1.255)
Drinking sessions per week							
0	5 016 718	116 123	40 915 000	2.838	1.111 (1.093–1.129)	1.081 (1.064–1.099)	1.059 (1.041–1.076)
1	2 185 917	27 371	18 031 496	1.518	0.900 (0.884–0.917)	0.933 (0.916–0.950)	0.927 (0.910–0.944)
2	1 271 588	19 721	10 450 497	1.887	1 (reference)	1 (reference)	1 (reference)
3	710 698	13 916	5 806 286	2.397	1.118 (1.094–1.142)	1.087 (1.063–1.111)	1.090 (1.067–1.114)
4	221 590	5160	1 802 335	2.863	1.219 (1.182–1.256)	1.164 (1.129–1.201)	1.170 (1.134–1.206)
5	151 407	4307	1 223 732	3.520	1.331 (1.287–1.375)	1.256 (1.215–1.298)	1.261 (1.220–1.304)
6	79 403	2868	634 119	4.523	1.417 (1.362–1.474)	1.333 (1.281–1.386)	1.339 (1.288–1.393)
7	139 635	6363	1 097 395	5.798	1.510 (1.468–1.554)	1.412 (1.373–1.453)	1.416 (1.376–1.457)
Amount of alcohol per drinking session (g)							
0 g (non-drinker)	5 016 718	116 123	40 915 000	2.838	1.054 (1.039–1.069)	1.037 (1.022–1.052)	1.012 (0.997–1.027)
≤32 g	1 740 348	32 708	14 249 667	2.295	0.996 (0.980–1.012)	1.012 (0.995–1.028)	1.000 (0.983–1.016)
≤56 g	1 596 414	27 665	13 079 981	2.115	1 (reference)	1 (reference)	1 (reference)
≤112 g	1 130 233	15 389	9 301 195	1.655	0.927 (0.908–0.945)	0.938 (0.919–0.956)	0.941 (0.923–0.960)
>112 g	293 243	3944	2 415 018	1.633	1.005 (0.972–1.039)	1.011 (0.978–1.046)	1.016 (0.983–1.051)

Multivariate Model 1: HRs are adjusted for age and sex.
Multivariate Model 2: HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, and dyslipidaemia.
Multivariate Model 3: HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, dyslipidaemia, heart disease (coronary artery disease or heart failure), and sleep apnoea.
HR, hazard ratio.

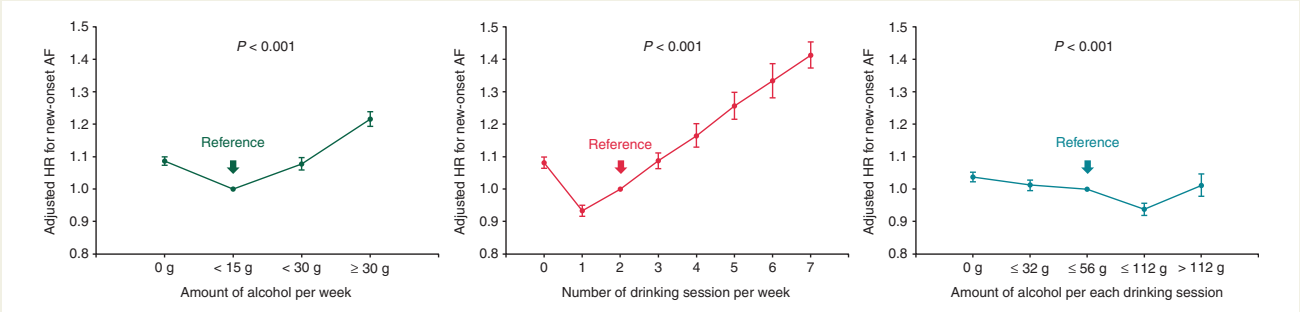

Figure 2 The risk of new-onset AF according to alcohol intake pattern. The amount of alcohol intake per week and number of drinking session per week were significant risk factors for new-onset AF. There was a statistically significant trend towards decreased risk of new-onset AF as the amount of alcohol consumption per drinking session increased. HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, and dyslipidaemia. AF, atrial fibrillation; HR, hazard ratio.

Alcohol and new-onset atrial fibrillation

Heavy alcohol intake is an established risk factor for new-onset AF.[7,8,13] Based on the Framingham Heart study data, weekly alcohol intake of more than 36 g per day (252 g per week) was associated with a 34% increased risk of new-onset AF.[13,14] However, the study did not show any increased risk of new-onset AF in mild or moderate drinkers, probably due to an insufficient sample size.[13] Subsequent studies also failed to demonstrate any associations between mild to moderate drinking and the development of new-onset AF, especially in women.[15] A recent meta-analysis revealed that moderate drinkers are also at higher risk of new-onset AF compared with non-drinkers.[8] Our study, which included a single cohort containing the largest number of patients, longest patient-year follow-up, and most new-onset AF cases, demonstrated that moderate and heavy drinking are

Table 3 Subgroup analysis according to sex status and age: weekly alcohol intake

	Subgroup	Weekly alcohol intake (g)	*N*	Event number	Patient* year	Incidence	Multivariate Model 1 (HR)	Multivariate Model 2 (HR)	Multivariate Model 3 (HR)
Sex	Male	Non-drinker (0 g)	1 707 780	44 569	13 752 782	3.241	1.073 (1.058–1.089)	1.050 (1.035–1.065)	1.037 (1.022–1.052)
		Mild drinker (0 < g < 105)	2 148 445	37 585	17 607 743	2.135	1 (reference)	1 (reference)	1 (reference)
		Moderate drinker (105 ≤ g < 210)	854 406	16 234	6 986 097	2.324	1.103 (1.083–1.123)	1.077 (1.059–1.097)	1.091 (1.071–1.111)
		Heavy drinker (≥210 g)	632 545	14 349	5 143 048	2.790	1.273 (1.248–1.297)	1.215 (1.193–1.238)	1.238 (1.214–1.262)
	Female	Non-drinker (0 g)	3 308 938	71 554	27 162 218	2.634	1.251 (1.225–1.277)	1.139 (1.115–1.164)	1.122 (1.098–1.146)
		Mild drinker (0 < g < 105)	988 109	10 144	8 178 539	1.240	1 (reference)	1 (reference)	1 (reference)
		Moderate drinker (105 ≤ g < 210)	96 557	990	798 447	1.240	1.097 (1.028–1.171)	1.032 (0.966–1.102)	1.039 (0.973–1.109)
		Heavy drinker (≥210 g)	40 176	404	331 985	1.217	1.121 (1.015–1.238)	1.015 (0.919–1.122)	1.023 (0.926–1.131)
Age (years)	20–39	Non-drinker (0 g)	1 102 729	4964	9 142 148	0.513	1.034 (0.994–1.076)	1.061 (1.020–1.105)	1.057 (1.016–1.101)
		Mild drinker (0 < g < 105)	1 344 748	5889	11 158 114	0.528	1 (reference)	1 (reference)	1 (reference)
		Moderate drinker (105 ≤ g < 210)	382 053	1983	3 165 775	0.626	1.094 (1.010–1.152)	1.056 (1.003–1.112)	1.057 (1.004–1.113)
		Heavy drinker (≥210 g)	253 888	1548	2 099 474	0.737	1.283 (1.213–1.358)	1.209 (1.142–1.280)	1.211 (1.144–1.282)
	40–64	Non-drinker (0 g)	2 977 003	51 643	24 538 659	2.105	0.999 (0.983–1.015)	1.012 (0.996–1.028)	1.002 (0.986–1.018)
		Mild drinker (0 < g < 105)	1 581 448	27 105	13 010 621	2.083	1 (reference)	1 (reference)	1 (reference)
		Moderate drinker (105 ≤ g < 210)	510 614	10 740	4 176 901	2.571	1.149 (1.124–1.175)	1.104 (1.079–1.129)	1.111 (1.086–1.137)
		Heavy drinker (≥210 g)	368 959	9004	3 004 955	2.996	1.306 (1.275–1.338)	1.229 (1.199–1.259)	1.239 (1.209–1.269)
	≥65	Non-drinker (0 g)	936 986	59 786	7 234 193	8.264	0.998 (0.979–1.018)	0.996 (0.977–1.016)	0.985 (0.966–1.004)
		Mild drinker (0 < g < 105)	210 358	14 735	1 617 548	9.110	1 (reference)	1 (reference)	1 (reference)
		Moderate drinker (105 ≤ g < 210)	58 296	4501	441 868	10.186	1.087 (1.051–1.124)	1.067 (1.032–1.104)	1.078 (1.042–1.115)
		Heavy drinker (≥210 g)	49 874	4201	370 605	11.336	1.194 (1.154–1.236)	1.174 (1.134–1.215)	1.190 (1.149–1.231)

Multivariate Model 1: HRs are adjusted for age and sex.
Multivariate Model 2: HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, and dyslipidaemia.
Multivariate Model 3: HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, dyslipidaemia, heart disease (coronary artery disease or heart failure), and sleep apnoea.
HR, hazard ratio.

Table 4 Subgroup analysis according to sex status and age: frequency of drinking

	Subgroup	Drinking session per week	Incidence	Multivariate Model 1	Multivariate Model 2
Sex	Male	0	3.241	1.048 (1.029–1.067)	1.031 (1.013–1.050)
		1	1.696	0.921 (0.902–0.940)	0.916 (0.897–0.935)
		2	2.040	1 (reference)	1 (reference)
		3	2.576	1.091 (1.066–1.116)	1.095 (1.070–1.120)
		4	3.020	1.162 (1.125–1.199)	1.168 (1.131–1.205)
		5	3.710	1.253 (1.211–1.297)	1.261 (1.219–1.305)
		6	4.723	1.322 (1.270–1.377)	1.332 (1.279–1.387)
		7	6.227	1.407 (1.365–1.449)	1.418 (1.376–1.460)
	Female	0	2.634	1.137 (1.091–1.185)	1.117 (1.072–1.164)
		1	1.160	0.981 (0.936–1.027)	0.977 (0.933–1.024)
		2	1.225	1 (reference)	1 (reference)
		3	1.336	1.008 (0.939–1.082)	1.011 (0.942–1.085)
		4	1.627	1.134 (1.010–1.272)	1.135 (1.011–1.273)
		5	1.888	1.158 (1.014–1.322)	1.161 (1.017–1.325)
		6	2.466	1.238 (1.043–1.469)	1.242 (1.047–1.473)
		7	2.694	1.161 (1.039–1.298)	1.158 (1.036–1.294)
Age (years)	20–39	0	0.513	1.015 (0.965–1.067)	1.009 (0.960–1.061)
		1	0.520	0.947 (0.903–0.994)	0.946 (0.902–0.992)
		2	0.601	1 (reference)	1 (reference)
		3	0.658	1.056 (0.989–1.128)	1.056 (0.989–1.128)
		4	0.710	1.117 (1.002–1.245)	1.119 (1.004–1.248)
		5	0.806	1.259 (1.094–1.449)	1.258 (1.093–1.448)
		6	0.908	1.410 (1.132–1.757)	1.404 (1.127–1.749)
		7	0.724	1.164 (0.918–1.475)	1.162 (0.916–1.473)
	40–64	0	2.105	0.976 (0.955–0.997)	0.964 (0.943–0.985)
		1	1.912	0.940 (0.918–0.962)	0.935 (0.913–0.957)
		2	2.260	1 (reference)	1 (reference)
		3	2.589	1.060 (1.031–1.090)	1.063 (1.034–1.093)
		4	2.857	1.119 (1.077–1.163)	1.123 (1.080–1.168)
		5	3.236	1.190 (1.141–1.241)	1.197 (1.147–1.248)
		6	3.492	1.208 (1.145–1.276)	1.215 (1.152–1.283)
		7	3.750	1.197 (1.147–1.250)	1.204 (1.154–1.257)
	≥65	0	8.264	0.990 (0.960–1.021)	0.975 (0.946–1.006)
		1	8.566	0.961 (0.926–0.997)	0.955 (0.921–0.992)
		2	9.309	1 (reference)	1 (reference)
		3	9.740	1.032 (0.989–1.076)	1.036 (0.993–1.081)
		4	10.294	1.075 (1.016–1.139)	1.081 (1.021–1.145)
		5	10.506	1.093 (1.030–1.160)	1.098 (1.035–1.166)
		6	10.908	1.114 (1.048–1.184)	1.124 (1.057–1.195)
		7	11.568	1.172 (1.123–1.223)	1.181 (1.132–1.233)

Multivariate Model 1: HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, and dyslipidaemia.
Multivariate Model 2: HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, dyslipidaemia, heart disease (coronary artery disease or heart failure), and sleep apnoea.

associated with an increased risk of new-onset AF in men but not in women, which is in accordance with the findings of previous studies. The current study also showed that non-drinkers are at an increased risk of developing new-onset AF compared with mild drinkers, a novel finding that has not been reported in previous studies to our knowledge.

Frequent drinking vs. binge drinking

Our study demonstrated that the number of drinking sessions per week is an important risk factor for new-onset AF that was independent from the total amount of weekly alcohol intake. Patients who drink everyday represented the highest risk group and those who drink once per week were the lowest risk group for new-onset AF in

Table 5 Impact of frequent drinking vs. binge drinking

	Weekly alcohol intake (g)	Subgroup	N	Event number	Patient*year	Incidence	Multivariate Model 1 (HR)	Multivariate Model 2 (HR)	Multivariate Model 3 (HR)
Frequency of drinking	<210	0 (non-drinker)	5 016 718	116 123	40 915 000	2.838	1.184 (1.170–1.198)	1.128 (1.114–1.142)	1.109 (1.096–1.123)
		1–2 drinking sessions per week	3 356 933	45 982	27 651 098	1.663	1 (reference)	1 (reference)	1 (reference)
		3–4 drinking sessions per week	612 916	14 268	4 986 342	2.861	1.247 (1.223–1.270)	1.178 (1.156–1.200)	1.185 (1.163–1.207)
		≥5 drinking sessions per week	117 668	4703	933 386	5.039	1.449 (1.406–1.493)	1.343 (1.303–1.384)	1.344 (1.304–1.385)
	≥210	1–2 drinking sessions per week	100 572	1110	830 895	1.336	1.011 (0.952–1.073)	1.005 (0.947–1.067)	1.015 (0.956–1.077)
		3–4 drinking sessions per week	319 372	4808	2 622 278	1.834	1.134 (1.101–1.168)	1.083 (1.051–1.116)	1.097 (1.064–1.130)
		≥5 drinking sessions per week	252 777	8835	2 021 861	4.370	1.560 (1.525–1.597)	1.428 (1.396–1.461)	1.445 (1.412–1.479)
Amount of alcohol per drinking session	<210	0 (non-drinker)	5 016 718	116 123	40 915 000	2.838	1.058 (1.045–1.072)	1.026 (1.013–1.039)	1.013 (1.000–1.026)
		≤32 g per drink	1 740 348	32 708	14 249 667	2.295	1 (reference)	1 (reference)	1 (reference)
		≤56 g per drink	1 470 073	22 748	12 074 172	1.884	0.948 (0.932–0.965)	0.942 (0.926–0.958)	0.953 (0.937–0.969)
		>56 g per drink	877 096	9497	7 246 987	1.310	0.818 (0.800–0.837)	0.836 (0.817–0.856)	0.848 (0.829–0.868)
	≥210	≤56 g per drink	126 341	4917	1 005 809	4.889	1.380 (1.339–1.422)	1.280 (1.242–1.320)	1.301 (1.262–1.341)
		>56 g per drink	546 380	9836	4 469 225	2.201	1.111 (1.086–1.136)	1.068 (1.044–1.093)	1.087 (1.062–1.112)

Multivariate Model 1: HRs are adjusted for age and sex.
Multivariate Model 2: HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, and dyslipidaemia.
Multivariate Model 3: HRs are adjusted for age, sex, smoking, regular physical activity, social income, body mass index, hypertension, diabetes mellitus, dyslipidaemia, heart disease (coronary artery disease or heart failure), and sleep apnoea.
HR, hazard ratio.

this investigation, respectively. Again, our study revealed that non-drinkers were at an increased risk of new-onset AF compared with those who drink once or twice per week. Furthermore, assuming an equal number of drinking sessions per week, the absolute amount of alcohol did not have any significant influence on the development of new-onset AF.

In contrast to the number of drinking sessions, the amount of alcohol intake per each drinking session was inversely associated with the risk of new-onset AF. When the cohort was stratified into those who drink less or more than 210 g per week, there was a tendency for a decreased risk of new-onset AF as the amount of alcohol intake per drinking session increased, suggesting that it is frequent drinking and not binge drinking that is responsible for the development of new-onset AF.

Mechanism

The underlying pathophysiology linking alcohol consumption and the development of new-onset AF largely remains unclear. Suggested mechanisms include a decreased atrial effective refractory period,[16] a trigger effect,[17] increased adrenergic activity,[18] and direct cardiotoxic effect.[10] In an animal study, porcine models demonstrated that acute alcohol injection increased the inducibility of AF.[11] Our study revealed that frequent drinking is more dangerous than infrequent binge drinking with regard to AF. If alcohol consumption is capable of triggering AF or increasing the inducibility of AF, multiple drinking episodes might induce more AF episodes, either symptomatic or asymptomatic. Since AF begets AF, these repetitive episodes of AF provoked by alcohol consumption might lead to the development of overt new-onset AF. The association between alcohol intake and increased risk of new-onset AF can also be explained by blood pressure elevation, obesity, and sleep disturbance caused by alcohol consumption which are all known risk factors for new-onset AF.[19,20] Our study showed higher blood pressure and body mass index in moderate to heavy drinkers (*Table 2*). Frequent drinking can provoke repetitive sleep disturbance which can explain the strong association between frequent drinking and new-onset AF observed in our study.

The protective effect of mild drinking observed in our study warrants further validation. At this point, it is not clear as to whether such a protective effect is a true beneficial effect of mild drinking or a mere confounding effect of unmeasured variables.

Clinical implications

Atrial fibrillation is a disease with multiple dreadful complications and a resulting significantly impaired quality of life, therefore, promoting an enormous health care burden. Standard medical practices to prevent such complications and improve quality of life are often expensive and may require lifelong treatment. The prevention of AF itself rather than its complications should be our first priority. There are known modifiable risk factors associated with the increased risk of new-onset AF such as hypertension, diabetes mellitus, obesity, dyslipidaemia, and obstructive sleep apnoea.[6] Heavy alcohol consumption is also a potentially correctable risk factor for new-onset AF. However, recommendations regarding alcohol consumption have focused on reducing the absolute amount of alcohol rather than drinking

frequency.[6] Our study suggests that reducing drinking frequency might also be important to reduce the overall burden of AF in a given population.

Limitations

The current study has several limitations. First, since our study was an administrative database-based analysis, the overall results might have been contaminated by coding inaccuracies although our coding strategy was validated in multiple previous studies.[12] There is a possibility of missing asymptomatic paroxysmal AF episodes in both screening and follow-up period. Second, the classification of AF according to type (e.g. paroxysmal and non-paroxysmal) was not possible. Third, our data are based on East Asian patients, so caution is required when applying our results to other ethnic groups. Fourth, alcohol intake habit was measured only once. Multiple measurement of alcohol intake habit will provide important information regarding whether reducing alcohol consumption amount and drinking frequency will have a protective effect.

Conclusion

The frequency of drinking is a significant risk factor for new-onset AF, whereas the amount of alcohol consumed per each drinking session had a minimal if any effect. Dividing alcohol consumption to avoid binge drinking may not be an appropriate strategy for preventing new-onset AF. The preventive effect of mild drinking observed in this study requires further validation.

Supplementary material

Supplementary material is available at *Europace* online.

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