**The cumulative burden of alcohol consumption and the risk of incident atrial fibrillation in young adults: a nationwide population-based cohort study**

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**Abstract**

**Background/ Purpose:** Guidelines recommend that all risk factors for early onset atrial fibrillation (AF) (including lifestyle factors) needs to be proactively managed, considering the disease’s poor prognosis. Not much is known about the effect of cumulative alcohol intake on the risk of AF in young adults aged 20 to 39 years, especially amongst heavy drinkers. We examined how cumulative alcohol consumption burden across 4 years affects the risk of incident AF in young adults.

**Methods:** Using the National Health Insurance Service database, 1,537,836 adults aged 20-39 years without prior prevalent AF who underwent 4 serial annual health examinations between 2009 and 2012 were identified. A cumulative alcohol consumption burden for 4 years was calculated by assigning 1 point to more than moderate drinking (≥105g of alcohol/week) each year. Additionally, a semi-quantitative cumulative burden was calculated by assigning 0, 1, 2, and 3 points to non, mild (<105g/week), moderate (105-210g/week), and heavy (≥210g/week) drinking, respectively. The primary outcome was incident AF during follow-up.

**Results:** During a median follow-up of 5.6±1.2 years, AF was newly diagnosed in 3,066 participants (0.36 per 1000 person-years). Subjects with cumulative burden of 4 points who continued more than moderate drinking for 4 years showed a 25% higher risk of AF compared to 0-point-subjects who kept non to mild drinking across 4 years. Subjects with 1 point and 3 points also showed increased risks of AF by 14% and 16%. In a semi-quantitative analysis, subjects who sustained heavy drinking for consecutive 4 years were associated with a 47% higher risk of AF compared to those who remained non-drinkers across 4 years.

**Conclusions:** Persistent moderate to heavy drinking and higher cumulative alcohol consumption burden might increase the risk of AF even in young adults aged 20-39. Meticulous screening for AF should be considered in young adults with a heavy alcohol drinking habit.

**Keywords:** alcohol consumption, atrial fibrillation, cumulative burden, nationwide population-based cohort

**Introduction**

Despite its lower prevalence in the young population, atrial fibrillation (AF) and AF-related complications such as stroke in the young population are associated with poor clinical outcomes (1–4). In addition, AF is a disease that recurs well even after treatment, for example, the recurrence rate reaches almost 50% despite treatments including cardioversion and antiarrhythmic drugs (5). Considering the long life expectancy of the young population and that active social roles are to be performed in this age group, awareness of AF prevention is necessary.

Alcohol is a well-known non-genetic risk factor for AF development. (6–8) Several studies have been conducted on the mechanism by which alcohol induces AF, and one of the potential mechanisms is that sinus tachycardia caused by alcohol-induced autonomic imbalance leads to AF (9). Changes in cardiac structure and function such as cardiomyopathy and atrial remodeling caused by excessive drinking are also thought to have an effect (10–13), and it was also suggested that high blood pressure, obesity (14), and heart failure (10,15) linked to excessive alcohol consumption, are also risk factors for incident AF.

While heavy drinking among young adults, especially those between ages 18-29, is one of the serious social issues that many countries are paying attention to (16–18), relatively few studies of the relationship between AF and alcohol consumption have been conducted in this young population. Even among studies that have explored AF as a rare but clinically important disease in the young population, the age criteria for ‘young age’ as defined by the authors were under 65 years in the study by Sankaranarayanan *et al.* (19), or under 60 (De With *et al.*(20)), and under 45 years (Segev *et al.*(21)) and the proportion of subjects between ages 18-29 who consume the most alcohol was small. Additionally, questions like how much cumulative amount of alcohol consumption over years increased the risk of AF, and whether there is a increase in the risk of AF in continuous drinking over years were unanswered, since most previous studies cross-sectionally identified the subjects’ alcohol consumption.

Drinking habits can be sufficiently improved with education and awareness, and is therefore a modifiable risk factor of AF. In this study, we investigated the impact of 4-years’ cumulative burden of alcohol consumption on the risk of incident AF in the young adults aged 20-39 years, using a nationwide population-based cohort.

**Methods**

*Data source*

We used data from the Korean National Health Information Database (NHID) for this study. The Korean National Health Insurance System (NHIS) is a social medical assistance insurance that is compulsory for Korean citizens, with over 51 million subscribers as of 2019. (22) The general national health screening examination is conducted annually or biennially for citizens over the age of 20 years. In addition to physical measurements, laboratory tests (includes fasting blood glucose, lipid profiles, and serum creatinine, etc.) and a self-reported lifestyle questionnaire is obtained. NHID also holds all the data from in-patient and outpatient medical claims of the subscribers, including prescriptions, procedures and surgery records, and information on insurance premium payment. (23) This study was exempted from review by the Seoul National University Hospital Institutional Review Board (E-2107-106-1235).

*Study population*

The flowchart of enrollment of the study population is presented in **Figure 1**. Young adults aged between 20 and 39 years who underwent 4 consecutive health screening examinations provided by the Korean NHIS from 2009 to 2012 were identified for the analysis. Subjects with prevalent AF before the last (4th) health examination and those with missing values in covariates among 4 health examinations were excluded.

*Definition of cumulative burden of alcohol consumption*

The alcohol consumption of each participant was investigated through the self-reported questionnaire at each health examination. The self-reported questionnaire and the calculation regarding the alcohol content in standard drink is presented in **Supplementary Methods**. Briefly explaining, the calculated alcohol content in one standard drink was 7.5g (12). We defined less than 105g (7.5g\*14 drinks, equivalent to low-risk drinking) of weekly alcohol consumption as mild drinking, more than 210g of weekly alcohol (twice the low-risk drinking) as heavy drinking, and 105g to 210g of weekly alcohol as moderate drinking.

To operationally define the cumulative burden of alcohol consumption, we assigned 1 point to each moderate to heavy drinking (>105g/week). Therefore, subjects were categorized into 5 groups according to their cumulative burden of alcohol consumption in 4-year (0, 1, 2, 3, and 4).

Additionally, to evaluate a dose-response relationship between the amount of alcohol consumption and the risk of AF, more stratified scoring for alcohol consumption burden was conducted. The novel semi-quantitative cumulative alcohol consumption burden was calculated by assigning 1 point for mild drinking, 2 points for moderate drinking, and 3 points for heavy drinking: using the previously established definitions for mild, moderate, and heavy drinking. (Mild drinking, <105g/week, moderate drinking, 105-210g/week, and heavy drinking, ≥210g/week.) Subjects were then categorized into 13 groups according to the semi-quantitative cumulative alcohol consumption burden for 4 years (0 through 12). (For detailed study design, refer to **Figure 2.**)

*Covariates*

Participants’ age, sex, underlying comorbidities, body mass index (BMI), smoking status, physical activity, and low income were included as covariates. All covariates were identified based on the information collected on the index (4th) health examination).

Comorbidities of hypertension, diabetes mellitus (DM), dyslipidemia, heart failure (HF), chronic obstructive pulmonary disease (COPD), thyroid disease, peripheral artery disease (PAD), prior myocardial infarction (MI), prior ischemic stroke, sleep apnea, and chronic kidney disease (CKD) were identified using the operational definitions according to International Classification of Disease, 10th Revision (ICD-10) codes. Detailed definitions are presented in **Supplementary Table 1**. We defined obesity as BMI>25kg/m2 (24). Smoking status (never-, ex-, and current smoker) and physical activity were assessed through the self-reported questionnaire. Performing regular physical activity was defined as exercising in moderate-intensity for more than 5 times a week or in vigorous-intensity more than 3 times a week (25). Participants who pay the bottom 20% of health insurance premiums for the entire Korean population were defined as a low-income group.

*Study outcome and follow-up*

The primary endpoint of the study was the diagnosis of new-onset AF during follow-up. We ascertained AF using ICD-10 codes I480–I484 and I489, and defined incident AF as either case in which the diagnostic code for AF was claimed at least once during hospitalization or twice in outpatient visits. (23) Recognizing AF by ICD-10 codes was validated by a study of Lee et al. (26), which confirmed that the positive predictive value of defining AF by ICD-10 codes reached 94.1%. We designated the last health examination date as the index date. Participants were followed up from the index date to the date of the new-onset AF, death, or the end of the follow-up (31st December 2018), whichever came first.

**Statistical analysis**

Continuous variables were expressed as mean ± standard deviation, and the categorical variables were shown in numbers (percentages). One-way analysis of variance (ANOVA) and the chi-square test were conducted to evaluate the baseline differences among groups categorized by 4 years’ cumulative alcohol consumption burden.

The crude incidence rate (IR) of new-onset AF was calculated as the number of events per 1000 person-years (PY). A cumulative incidence of AF by cumulative alcohol consumption burdens was evaluated with survival analysis and log-rank test and was displayed using Kaplan-Meier survival curves.

Using a multivariable Cox regression model, we analyzed the association between cumulative alcohol consumption burdens during 4-year and the risk of incident AF. A model adjustment was made for covariates of age, sex, comorbidities, including hypertension, DM, dyslipidemia, HF, COPD, thyroid disease, PAD, prior MI, prior ischemic stroke, sleep apnea, and CKD, BMI, smoking status (non-, ex-, and current smokers), performing regular physical activity and low-income. The risks for incident AF according to different cumulative alcohol consumption burdens were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The level of significance was set at 0.05, and all analyses were two-sided. We used SAS version 9.4 (SAS Institute, Cary, NC) for statistical analyses.

*Subgroup analyses*

We performed subgroup analyses and interaction tests evaluating the potential impact of age, sex, comorbidities (hypertension, DM, dyslipidemia, HF, COPD, thyroid disease, PAD, prior MI, prior ischemic stroke, sleep apnea, and CKD), BMI, smoking status, performing regular physical activity, and low-income. P for interaction less than 0.1 was considered significant.

*Sensitivity analysis*

To provide complementary analysis for apparently healthy young adults, we conducted a sensitivity analysis in a population without HF, prior MI, and prior ischemic stroke. In addition, considering the potential impact of incident HF, MI or stroke during the follow-up period on the risk of incident AF, subjects were censored when these cardiovascular adverse events occurred.

**Results**

A total of 1,537,836 participants (mean age 29.5±4.1 years, 71.5% men) were included in the final analysis (**Figure 1**). According to 4-year cumulative burden of alcohol consumption stratified by moderate to heavy drinking or not, 57.8% (n=889,382) were in burden 0 group, 13.2% (n=203,374) in burden 1 group, 9.6% (n=148,087) in burden 2 group, 9.4% (n=144,023) in burden 3 group, and 9.9% (n=152,970) in burden 4 group. Baseline characteristics of the study population are presented in **Table 1**. The proportion of men and current smokers were significantly higher in the groups with a higher cumulative alcohol consumption burden. Regarding underlying comorbidities, the prevalence of hypertension and dyslipidemia tended to increase with the increasing cumulative alcohol consumption burden. The prevalence of obesity also increased according to the increase of cumulative alcohol consumption burden.

*4-year cumulative alcohol consumption burden and the risk of incident AF*

During mean 5.6±1.2 years of follow-up duration (8,533,037 PYs of follow-up), 3,066 participants were diagnosed with new-onset AF (IR, 0.36 per 1000 PY). The number of events, crude IR, unadjusted hazard ratios (HRs), and Kaplan-Meier curves for incidence probability of AF according to cumulative alcohol consumption burden are presented in **Table 2** and **Figure 3**. Generally, subjects with a higher cumulative burden of alcohol consumption during a 4-year showed a higher IR for AF than those who sustained non to mild drinking (burden 0). Adjusted HRs for the risk of new-onset AF according to the cumulative alcohol consumption burden evaluated on 4-year consecutive health examinations are presented in **Table 2** and **Figure 4A**. Subjects with burdens 1, 3, and 4 were associated with 14%, 16%, and 25% increase in the risk of AF compared to the burden 0 group, respectively (**Table 2** and **Figure 4A**).

*Semi-quantitative cumulative alcohol consumption burdens and the risk of incident AF*

Calculating the semi-quantitative cumulative alcohol consumption burden across 4 years, subjects who sustained heavy drinking (3 points) over 4 years (semi-quantitative burden 12) showed a higher risk of incident AF by 47% compared to those who sustained non-drinking (semi-quantitative burden 0) (**Table 2** and **Figure 4B**). Subjects with semi-quantitative burden 11, who mostly continued heavy drinking but reported moderate drinking for one year, was associated with a 31% higher risk of AF compared to those with a semi-quantitative burden of 0 (**Table 2** and **Figure 4B**).

*Subgroup analyses*

The results of subgroup analyses according to subjects’ age, sex, comorbidities including hypertension, DM, dyslipidemia, HF, COPD, thyroid disease, PAD, prior MI, prior ischemic stroke, sleep apnea, and CKD, BMI, smoking status, performing regular exercise, and low-income are presented in **Supplementary Table 2**. There were no significant interactions between various subgroups and the associations between cumulative alcohol consumption burden and the risk of AF, except for sex subgroup (p-for-interaction = 0.07). Only in men were the main results consistently observed.

*Sensitivity analysis*

We analyzed the association between cumulative alcohol consumption burden and incident AF in apparently healthy young adults without previous history and new occurrence of HF, MI or ischemic stroke during follow-up. In this sensitivity analysis, the results were consistent with the main result. The risks of AF were higher in subjects with burden 1 group (HR 1.15, 95% CI 1.03-1.29), burden 3 group (HR 1.18, 95% CI 1.04-1.34), and burden 4 group (HR 1.22, HR 1.08-1.38) than those with burden 0 group (**Supplementary Table 3**).

**Discussion**

In this study, we investigated the effect of cumulative alcohol consumption burden on the risk of incident AF in young adults. The principal findings of this study are summarised as follows: (1) the risk of AF was increased by 25% in subjects who kept moderate to heavy drinking for 4 years compared to those who sustained non to mild drinking; (2) persistent heavy drinking across 4 years was associated with a higher risk of AF by 47% compared with persistent non-drinking; and (3) the positive correlation between high cumulative alcohol consumption and higher risk of AF was consistently observed in apparently healthy young adults.

The prevalence and incidence of AF worldwide are increasing, and so are the healthcare costs due to the disease (27,28). The most likely reason for the increasing prevalence of AF is the overall aging population, which is a critical risk factor for incident AF and AF-related complications.(1,3,29–31) AF is also associated with various cardiovascular risk factors and comorbities, and multimorbidity is common amongst patients with AF, contributing to complications such as stroke and hearat failure [ref].

Nonetheless, AF can be challenging especially amongst the healthy young population without underlying cardiovascular diseases; however, drinking is also one of the risk factors for development of AF even amongst young people (6–8). Several mechanisms by which alcohol consumption triggers AF, have included stimulation of the sympathetic nervous system that promotes adrenaline secretion, parasympathetic modulation of autonomic tone, and slowing of interatrial electrical conduction concomitant with shorter atrial refractory period resulting in re-entry (13). In addition, structural changes in atria such as left atrial enlargement (11), and atrial tissue fibrosis (13) were also proposed as a possible pathophysiology.

Although some previous studies have already revealed the association of excessive drinking with increased risk of AF (6–8,32,33), there are limited data on the threshold amount of drinking, or drinking patterns and habits related to AF. Likewise, although some studies reported an opposing action of alcohol showing cardiovascular-protective effect of mild or moderate drinking (34,35), each of these studies used different criteria defining the amount of drinking, so that there has been no consensus on how much alcohol should be considered low or high-risk drinking (36). In our study, we further consolidated on these associations between alcohol intake and AF risk. The strength of this study lies in the study design, where we identified and enrolled a large number of young adults who had undergone health check-ups every year across 4 years. In light of the vast amount of collected data, we could evaluate the subjects’ cumulative burden of moderate to heavy drinking for a continuous period and gain detailed information on the cumulative amount of alcohol consumption across 4 years. Compared to previous studies with only cross-sectional estimation of the subjects’ alcohol consumption status (32,33), our study has evaluated the subjects longitudinally.

Another major novelty of our study is the application of two different concepts of cumulative alcohol burden. Analyzing the relationship between alcohol burdens that were defined by the two different methods, and the risk of AF, we confirmed that both persistent moderate to heavy drinking for 4 years and semi-quantitative cumulative alcohol consumption burden higher than 10 points in 4 years was significantly associated with a higher risk of AF. Interestingly, the only cumulative amount of alcohol higher than 10 points (11 and 12 points) was associated with a significant increase in AF risk. Subjects in these groups consumed over 2.5 points of alcohol per year on average over the studied 4 years, where 2.5 points of alcohol consumption indicating more than moderate (105-210g), but less than heavy (≥210g) drinking according to our operational definition. Alcohol intake in this range could represent a new threshold for average alcohol content over a 4-year period that increases AF risk and could be utilized as a reference in subsequent longitudinal studies.

Alcohol consumption among the young population is a global social problem that has steadily drawn attention. According to the World Health Organization report, 13.5% of the total deaths among the population aged 20-39 years are related to alcohol consumption. (17) In addition, young adults (ages 20-24 years) account for 48.5% of heavy episodic drinkers among all drinkers. (18) To our best knowledge, the present study included the largest number of young adults as subjects, especially those between ages 20 and 39, among studies on the same topic. While Lee *et al*. emphasized the favorable effect of alcohol abstinence in AF patients reducing the risk of ischemic stroke (37), another study on the effects of alcohol abstinence by Voskoboinik *et al*. have as well demonstrated a reduction in recurrence and a reduction in total disease burden in patients with AF (38). Choi *et al.* found that the risk of AF was reduced with alcohol abstinence in patients who were newly diagnosed with diabetes (39).

Given that AF induces fatal complications including stroke (40), that the prognosis is worse when AF is diagnosed at an early age (3), and that there is a positive relationship between alcohol consumption and AF, as well as that the risk of AF and stroke is lowered by alcohol abstinence under various circumstances (37,38) strongly suggests that we should educate young adults about the risk of AF and its strong association with drinking. Indeed, addressing excessive alcohol consumption is part of the holistic or integrated care approach to AF care [ref], with this approach being associated improved in improved clinical outcomes [ref].

*Limitations*

First, because diagnostic codes recorded in NHID are claimed by healthcare providers for medical billing and reimbursement and not for research, the disparity between the diagnostic code and the actual diagnosis may exist due to contamination or coding inaccuracy. There is also the possibility of over-or under-estimation of diagnosis since the analyses are based on novel operational definitions (8,23). Second, this study was conducted only on the Asian population, so caution is required when applying the study results to populations of other races. Third, alcohol consumption itself could be a risk factor for other risk factors of AF. Looking at the baseline characteristics of the subjects according to the 4-year alcohol burden of moderate to heavy drinking, we confirmed that there were more comorbidities such as hypertension, DM, and dyslipidemia in the higher cumulative alcohol burden groups. Subjects’ BMIs were higher in the higher burden groups as well. Although we went through adjustment steps in the analyses to correct the extensive influence of different comorbidities and body measurements, the severity of comorbidity or the level of management might not have been reflected in the correction. Fourth, the alcohol intake was surveyed based on a self-reported questionnaire, of which a recall bias may have intervened. Nevertheless, this method had already been adopted by numerous previous studies in which meaningful research results were obtained (7,33,41,42). Lastly, the proportion of drinkers, particularly of moderate to heavy drinkers, was fundamentally too small in female subjects. Therefore, it is not possible to conclusively state the relationship between alcohol consumption and AF in the young women population according to the results of this cohort alone.

**Conclusion**

Persistent moderate to heavy drinking and higher cumulative alcohol consumption burden might increase the risk of AF even in young adults. Meticulous screening for AF should be considered in young adults with a heavy drinking habit.

**Conflict of interest**

EKC: Research grants or speaking fees from Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daiichi-Sankyo, Dreamtech Co., Ltd., Medtronic, Samjinpharm, Sanofi-Aventis, Seers Technology, and Skylabs. GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

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**Figure legend**

Figure 1. Flowchart of the study

Figure 2. Study design

Figure 3. Kaplan-Meier curve according to 4-year alcohol burden