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Original Research

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Causal Association Between Alcohol Consumption and Atrial Fibrillation: A Mendelian Randomization Study

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AUTHOR'S SUMMARY

Previous observational studies presented a positive association between alcohol and atrial fibrillation (AF). However, previous studies using genetic polymorphisms on the causal relationship between alcohol consumption and AF have reported conflicting results. This study evaluated the causality between alcohol consumption and AF using the aldehyde dehydrogenase 2 (*ALDH2*) rs671 polymorphism. In 8,964 cohort participants, genetic analysis and Mendelian randomization analysis using the *ALDH2* genotypes showed a significant causal association between alcohol consumption and AF in men.

ABSTRACT

Background and Objectives: Previous observational studies presented a positive association between alcohol and atrial fibrillation (AF). However, previous studies using genetic polymorphisms on the causal relationship between alcohol consumption and AF have reported conflicting results. This study aimed to evaluate the causality between alcohol consumption and AF using the aldehyde dehydrogenase 2 (*ALDH2*) rs671 polymorphism, which is the genetic variant with the most potent effect on drinking behavior.
Methods: A total of 8,964 participants from the Dong-gu Study were included in the present study. The causal association between alcohol consumption and AF was evaluated through a Mendelian randomization (MR) analysis using the *ALDH2* rs671 polymorphism as an instrumental variable.
Results: No significant relationship between alcohol consumption and AF was found in the observational analysis. However, the genetic analysis using the *ALDH2* polymorphism showed a significant association in men. In the MR analysis, genetically predicted daily alcohol consumption was positively related to AF.
Conclusions: MR analysis revealed a significant association between the amount of alcohol consumption and AF, which suggests that the association may be causal.

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Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions
Conceptualization: Shin MH; Formal analysis: Yang JH, Shin MH; Investigation: Kweon SS, Lee YH, Choi SW, Ryu SY, Nam HS, Park KS, Kim HY, Shin MH; Methodology: Shin MH; Supervision: Shin MH; Writing - original draft: Yang JH, Shin MH; Writing - review & editing: Yang JH, Jeong JA, Kweon SS, Lee YH, Choi SW, Ryu SY, Nam HS, Park KS, Kim HY, Shin MH.

Keywords: Alcohol drinking; Atrial fibrillation; Causality; Mendelian randomization analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, and its prevalence is increasing every year.[1)2)] AF causes stroke, congestive heart failure, and sudden cardiac death.[3)] The mortality and morbidity of AF, including increasing the frequency of hospitalization, place large socioeconomic burdens on society.[4)] Many risk factors for AF have been reported, such as aging, male sex, hypertension, obesity, sleep apnea; however one of the most important preventable risk factors is alcohol consumption.[5)]

Previous observational studies have shown that alcohol consumption affects the incidence of AF through different mechanisms depending on drinking behavior.[6)] Generally, previous observational studies used multivariate models adjusted for confounders to evaluate the association between alcohol consumption and AF.[7)] However, it is difficult to conclude causality from the results of observational studies because numerous factors, including individual characteristics such as socioeconomic status, lifestyle, and demographics, affect the pattern of drinking.[8)] For instance, it is impossible to correct for all confounders and to rule out reverse causation in observational studies.[9)]

One of the methods for evaluating causality between exposure and outcome is the instrumental variable (IV) method. When a variable is causally associated with the exposure, the outcome is affected only by the exposure; the variable is not associated with any confounders between the exposure and outcome, and the variable can be used as an IV substituting for the exposure.[10)] If some genetic polymorphisms are used as IVs which satisfy the assumptions, the method of analysis is called the Mendelian randomization (MR) method. As genetic polymorphisms cannot be affected by other factors, the analysis is performed under the assumption of random allocation according to genetic variants, and the results are relatively free from confounding and reverse causation.[11)]

Alcohol is metabolized through several stages after ingestion. The major pathway involves 2 enzymes: alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). First, ethanol is dehydrogenated to acetaldehyde by ADH. Thereafter, acetaldehyde is metabolized to acetate by ALDH.[12)] A functional single nucleotide polymorphism in the *ALDH2* rs671 gene results in the reduced function of ALDH and the accumulation of aldehyde after alcohol ingestion.[13)] The accumulated aldehyde cannot be removed from the body, and a syndrome called “Oriental flushing” occurs, consisting of a series of symptoms including facial flushing and nausea. These unpleasant symptoms prevent people who have the syndrome from drinking alcohol.[14)] Consequently, *ALDH2* polymorphism may be the most potent IV as the genetic predisposition for alcohol consumption.[15)]

Previous studies have used genetic variants to evaluate the relationship between alcohol and AF. In Japan, a case-control study in hospitalized patients showed an association between genetic polymorphism and AF.[5)] However, the dataset used in the study was not available for alcohol consumption, the effect size of alcohol on AF could not be estimated. Meanwhile, three genome-wide association studies that performed two-sample MR reported conflicting results. As all studies did not use the *ALDH2* gene as an IV, their results may not be applicable

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for the East Asian population.[16-18] In the present study, we performed the MR analysis using *ALDH2* rs671 to examine the causal association between alcohol and AF in Korea.

METHODS

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Chonnam National University Hospital (IRB No. I-2008-05-056). Informed consent was obtained from all participants when they were enrolled in baseline examination.

Subjects

The study participants were from the Dong-gu Study, which included residents of the Dong District, Gwangju, Korea. The cohort included 9,260 participants, and the baseline survey was conducted from May 2007 to July 2010.[19] From the cohort, 296 participants were excluded because of missing values in *ALDH2* rs671 genotypes, physical activity, alcohol drinking frequency, amount of alcohol consumption at one time, smoking history, height, weight, hypertension, diabetes, educational status, and AF. Finally, 8,964 subjects were included in this study.

Covariates

Information on age, physical activity, alcohol consumption in standard glasses per day, smoking history, body mass index (BMI), hypertension, diabetes, education status, history of coronary heart disease (CHD), high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG) and AF were obtained from the Dong-gu Study dataset. We defined physical activity as walking at least five times a week and for >30 minutes at a time. Alcohol consumption was estimated using the number of days of drinking alcohol per week and the number of standard glasses of alcohol consumed per drinking day. In addition, alcohol consumption was categorized into 4 categories; never drinker, former drinker, light to moderate drinker (<2 drinks/day in men, <1 drinks/day in women), and heavy drinker (≥2 drinks/day in men, ≥1 drinks/day in women).[20] The converted amount by beverage type was included in the question on the amount of alcohol consumption, preventing the participants from measuring their consumption differently for different beverage types. Smoking status was classified as never, former, or current. Participants who had smoked <5 packs in their lifetime were defined as never smokers. For the rest of the participants, the question "Do you smoke currently?" was used to distinguish between current smokers and former smokers. BMI was calculated using the measured height and weight, and the participants were categorized into the underweight, normal, overweight, and obesity groups according to the World Health Organization cutoff criteria.[21] Participants who were diagnosed or had a medication with hypertension or had a measured blood pressure of ≥140/90 mmHg were defined as having hypertension. Participants who were diagnosed or had a medication with diabetes or had a measured serum glucose level of ≥126 mg/dL were defined as having diabetes. Education status was divided into groups based on an education duration of >9 years.

Genotyping

Following the manufacturer's protocol, DNA was extracted with QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA, USA) from peripheral blood. As previously described,[22] rs671 was genotyped by high-resolution melting (HRM) analysis using a Rotor-Gene 6000 (Corbett Research, Sydney, Australia). The polymerase chain reaction (PCR) primers (forward,

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5′-TTGGTGGCTACAAGATGTCG-3′; reverse, 5′-CAGGTCCCACACTCACAGTTT-3′) produced a 97-bp amplicon. The reaction mixture was used for HRM and consisted of 200 nM PCR primer, 1 μM SYTO 9 fluorescent dye (Invitrogen, Carlsbad, CA, USA), 0.5 U F-Star Taq polymerase (BioFACT, Daejeon, Korea), and 40 ng genomic DNA in 10-μL reaction volumes. PCR was started at 95°C for 5 minutes, followed by 40 cycles of 95°C for 5 seconds and 58°C for 30 seconds.

Outcome measures

The participants underwent 12-lead electrocardiography using HP-PageWriter 200 M1771A (Hewlett Packard, Andover, MA, USA) at baseline survey. The recorded electrocardiograms were preliminary analyzed using the Philips 12-lead algorithm and potential cases of AF were identified by 2 cardiologists. In addition, participants who had been treated for AF before the baseline survey were classified as patients with AF.

Statistical analyses

Because alcohol consumption has significant differences between men and women,[23] sex stratification was implemented in all analyses. Since the frequency of the AA genotype was low, the GA and AA genotypes were combined. The characteristics of participants according to *ALDH2* genotypes were presented as the mean ± SD or number (%), compared using independent t-test or χ^2 test was conducted. Age adjusted prevalence of AF according to categorized alcohol consumption was presented using logistic regression. Simple logistic regression and multivariate logistic regression analyses were performed as observational analyses to identify the effect of alcohol consumption on AF. To assess the impact of 'sick quitter,' meaning that disease may alter health behavior, observational analyses were conducted in population without former drinkers as sensitivity analysis. In addition, to investigate the effect of heavy drinking on AF, sensitivity analysis was performed in which alcohol consumption were treated as categorical variable. To show the association between *ALDH2* polymorphism and AF, univariate and multivariate logistic regression analyses were conducted. Multivariate logistic regression models were adjusted for age, physical activity, smoking status, BMI category, hypertension, diabetes, and education status. In addition, in a sensitivity analysis to assess the pleiotropic effect between *ALDH2* genotypes and AF, we adjusted for the potential confounders or mediators such as CHD history, HDL, LDL, and log transformed TG. These variables were reported in the Phenoscanner as an *ALDH2* related phenotypes which is the database holding publicly available results from large-scale genome-wide association studies.[24][25] A 2-stage MR analysis was performed to evaluate the association between the genetically predicted daily alcohol consumption and AF in men because the difference in the amount of alcohol consumption between men and women was not significant according to *ALDH2* genotypes. In the first stage, to obtain genetically predicted log transformed alcohol consumption, linear regression analyses of alcohol consumption on the *ALDH2* genotypes were performed. Because alcohol consumption had a left-deviated distribution, the amount of alcohol consumption was used in the model, which was modified by adding the minimum amount of alcohol consumption and log transformation. In the second stage, the association between the back-transformed predicted amount of alcohol consumption and AF was estimated using a univariate and multivariate logistic regression model that included age, physical activity, smoking history, BMI, hypertension, diabetes, and education status. The same MR analyses were conducted as sensitivity analyses in participants excluding former drinkers. All analyses were performed using R (version 4.0.2; The R Foundation, Vienna, Austria).

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RESULTS

The characteristics of participants according to genotypes are presented in **Table 1**. The GG genotype group drank more alcohol and was younger than the GA/AA group in both sexes. Hypertension and diabetes were more prevalent in GG genotype group than GA/AA genotype group in men. There were more smokers in GG genotype group than GA/AA genotype group in women.

Figure 1 showed the age-adjusted prevalence of AF according to never drinker, former drinker, light to moderate drinker, and heavy drinker. The highest proportion of prevalent AF was observed in the former drinkers in both sexes. However, significant difference of age-adjusted prevalence of AF among alcohol consumption was shown only in women. There was no prevalent case of AF in women heavy drinkers.

Table 2 presents the association between the amount of alcohol consumption and AF in the observational analysis using logistic regression models. In a simple logistic regression, age, current smoking status and hypertension were associated with AF in men. Age, hypertension, and educational status were associated with AF in women. In adjusted model, no significant association was observed between the amount of alcohol consumption and AF in men (adjusted odds ratio [OR], 0.99; 95% confidence interval [CI], 0.90–1.08) and in women (adjusted OR, 0.38; 95% CI, 0.03–1.19). A sensitivity analysis excluding former drinkers yielded similar result (**Supplementary Table 1**). The association between categorized alcohol consumption and AF was presented in **Supplementary Table 2**. In men, alcohol consumption was not associated with AF. In women, former drinkers were associated with an increased risk of prevalent AF compared to never drinkers, while light to moderate drinker was not.

Table 1. Baseline characteristics of the study population according to *ALDH2* rs671 genotypes

Characteristics	Men			Women		
	GG (n=2,414)	GA/AA (n=1,163)	p value	GG (n=3,759)	GA/AA (n=1,628)	p value
Age (years)	65.7±8.0	67.1±7.9	<0.001	64.3±8.2	65.0±8.2	0.006
Physical activity (yes)	1,659 (68.7)	808 (69.5)	0.677			0.585
Drinks per day (glass/day)	2.0±2.6	0.4±1.0	<0.001	0.1±0.5	0.0±0.2	<0.001
Alcohol consumption category			<0.001			<0.001
Never drinker	192 (8.0)	494 (42.5)		2,058 (54.7)	1,329 (81.6)	
Former drinker	321 (13.3)	161 (13.8)		265 (7.0)	73 (4.5)	
Light to moderate drinker	1,121 (46.4)	455 (39.1)		1,299 (34.6)	217 (13.3)	
Heavy drinker	780 (32.3)	53 (4.6)		137 (3.6)	9 (0.6)	
Smoking history			0.757			0.010
Never	619 (25.6)	307 (26.4)		3,606 (95.9)	1,589 (97.6)	
Former	1,211 (50.2)	568 (48.8)		72 (1.9)	19 (1.2)	
Current	584 (24.2)	288 (24.8)		81 (2.2)	20 (1.2)	
BMI (kg/m^2)			0.097			0.269
Underweight	56 (2.3)	42 (3.6)		61 (1.6)	21 (1.3)	
Normal	1,477 (61.2)	725 (62.3)		2,016 (53.6)	911 (56.0)	
Overweight	836 (34.6)	377 (32.4)		1,510 (40.2)	634 (38.9)	
Obesity	45 (1.9)	19 (1.6)		172 (4.6)	62 (3.8)	
Hypertension (yes)	966 (40.0)	409 (35.2)	0.006	1,434 (38.1)	618 (38.0)	0.921
Diabetes (yes)	477 (19.8)	160 (13.8)	<0.001	475 (12.6)	204 (12.5)	0.950
Middle school (yes)	1,716 (71.1)	859 (73.9)	0.091	1,644 (43.7)	753 (46.3)	0.093
Atrial fibrillation (yes)	81 (3.4)	24 (2.1)	0.042	50 (1.3)	14 (0.9)	0.185

All values are presented as the mean ± SD or number (%). Independent t-test and χ^2 tests were conducted for continuous and categorical variables, respectively.
Alcohol consumption was categorized into 4 groups: never drinker, former drinker, light to moderate drinker (<2 drinks/day in men, <1 drink/day in women), and heavy drinker (≥2 drinks/day in men, ≥1 drink/day in women).
BMI was categorized into 4 groups: underweight (less than 18.5), normal (18.5–24.9), overweight (25.0–29.9), and obesity (30.0 or more).
ALDH2 = aldehyde dehydrogenase 2; BMI = body mass index.

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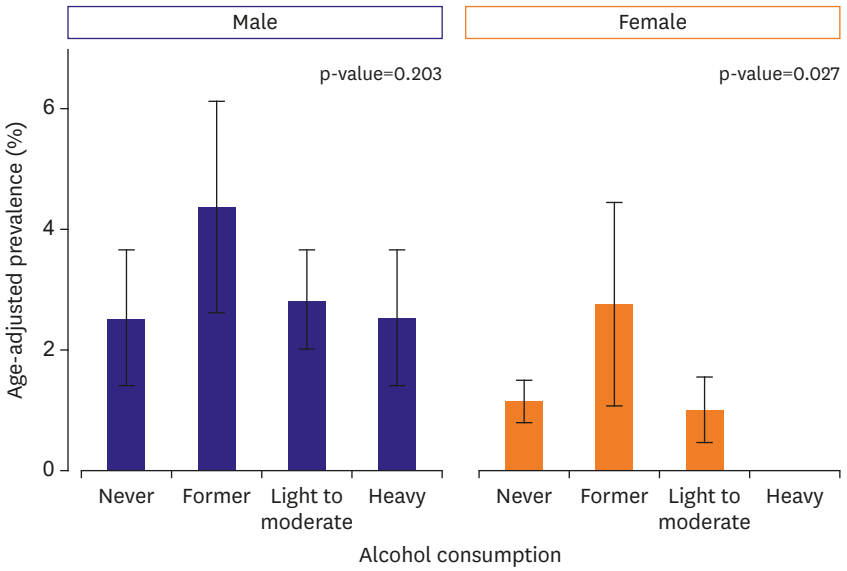

Figure 1. Age-adjusted prevalence of atrial fibrillation according to alcohol consumption.

Table 2. Association between alcohol consumption (drinks per day) and atrial fibrillation in the observational analysis

Variables	Men				Women			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Drinks per day (glass/day)	0.96 (0.87–1.04)	0.368	0.99 (0.90–1.08)	0.825	0.24 (0.01–1.00)	0.192	0.38 (0.03–1.19)	0.306
Age (years)	1.05 (1.02–1.07)	<0.001	1.04 (1.01–1.07)	0.004	1.07 (1.04–1.10)	<0.001	1.06 (1.02–1.09)	0.001
Physical activity (yes)	1.08 (0.71–1.67)	0.735	1.07 (0.70–1.66)	0.773	0.98 (0.59–1.63)	0.928	1.16 (0.70–1.96)	0.566
Smoking history								
Never vs. former	0.93 (0.61–1.45)	0.736	0.92 (0.59–1.43)	0.695	1.89 (0.31–6.18)	0.380	1.16 (0.18–3.93)	0.843
Never vs. current	0.41 (0.21–0.76)	0.007	0.47 (0.24–0.9)	0.027	0.84 (0.05–3.87)	0.865	0.85 (0.05–4.03)	0.877
BMI (kg/m^2)								
Normal vs. underweight	1.11 (0.27–3.06)	0.864	0.96 (0.23–2.71)	0.942	0.94 (0.05–4.41)	0.950	0.80 (0.04–3.87)	0.831
Normal vs. overweight	1.14 (0.75–1.70)	0.546	1.13 (0.73–1.72)	0.573	0.82 (0.48–1.38)	0.467	0.78 (0.45–1.30)	0.345
Normal vs. obesity	1.73 (0.41–4.83)	0.367	1.81 (0.43–5.21)	0.334	0.66 (0.11–2.16)	0.562	0.60 (0.10–2.00)	0.486
Hypertension (yes)	1.59 (1.08–2.35)	0.019	1.35 (0.90–2.04)	0.149	1.86 (1.13–3.06)	0.014	1.47 (0.88–2.47)	0.146
Diabetes (yes)	1.23 (0.75–1.95)	0.393	1.09 (0.66–1.75)	0.716	1.78 (0.92–3.19)	0.065	1.37 (0.70–2.50)	0.324
Middle school (yes)	0.71 (0.47–1.07)	0.096	0.7 (0.46–1.07)	0.089	0.56 (0.32–0.94)	0.034	0.83 (0.46–1.45)	0.512

Multivariate logistic regression models were adjusted for age, physical activity, smoking status, BMI category, hypertension, diabetes, and education status.
BMI = body mass index; CI = confidence interval; OR = odds ratio.

Table 3 presents the associations between *ALDH2* polymorphism and AF. In men, the GG genotype had a higher risk of AF (adjusted OR, 1.69; 95% CI, 1.08–2.74). In women, the association between *ALDH2* genotypes and AF was not significant (adjusted OR, 1.55; 95% CI, 0.88–2.93). After further adjustment of CHD history, HDL, LDL and log transformed TG, *ALDH2* genotype was associated with AF (adjusted OR, 1.71; 95% CI, 1.08–2.79) in men (**Supplementary Table 3**).

The results of MR analyses are shown in **Table 4**. The MR analysis was conducted in men, because there was a significant association between *ALDH2* polymorphism and AF only in men. Although the observational analyses did not show significant relationships, there was a positive relationship between predicted alcohol consumption and AF in univariate (OR, 3.00 [95% CI, 1.13–8.68]) and multivariate model (OR, 3.17 [95% CI, 1.18–9.24]). However, in a sensitivity analysis except former drinkers, this association was attenuated and remained significant in both univariate (OR, 2.05 [95% CI, 1.05–4.28]) and multivariate model (OR,

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Table 3. Association between atrial fibrillation and rs671 polymorphisms by sex

Variables	Men		Women	
	OR (95% CI)	p value	OR (95% CI)	p value
Unadjusted				
GG vs GA/AA	1.65 (1.06–2.67)	0.034	1.55 (0.88–2.93)	0.147
Adjusted				
GG vs GA/AA	1.69 (1.08–2.74)	0.028	1.66 (0.94–3.13)	0.098
Age (years)	1.04 (1.02–1.07)	0.002	1.06 (1.03–1.10)	<0.001
Physical activity (yes)	1.06 (0.70–1.65)	0.793	1.15 (0.69–1.94)	0.593
Smoking history				
Never vs. former	0.91 (0.59–1.42)	0.667	1.08 (0.17–3.65)	0.916
Never vs. current	0.47 (0.24–0.89)	0.026	0.72 (0.04–3.39)	0.750
BMI (kg/m^2)				
Normal vs. underweight	0.99 (0.24–2.81)	0.988	0.79 (0.04–3.80)	0.819
Normal vs. overweight	1.13 (0.74–1.72)	0.565	0.75 (0.44–1.26)	0.290
Normal vs. obesity	1.79 (0.42–5.14)	0.346	0.56 (0.09–1.89)	0.436
Hypertension (yes)	1.32 (0.88–2.00)	0.179	1.47 (0.88–2.47)	0.144
Diabetes (yes)	1.05 (0.63–1.68)	0.845	1.40 (0.72–2.55)	0.294
Middle school (yes)	0.71 (0.47–1.09)	0.110	0.85 (0.47–1.49)	0.582

Multivariate logistic regression models were adjusted for age, physical activity, smoking status, BMI category, hypertension, diabetes, and education status.
BMI = body mass index; CI = confidence interval; OR = odds ratio.

Table 4. Association between genetically predicted alcohol consumption (glass/day) and atrial fibrillation in men

Populations	No.	Model	OR (95% CI)	p value
Total population	3,577	Unadjusted	3.00 (1.13–8.68)	0.034
		Adjusted	3.17 (1.18–9.24)	0.028
F statistics = 864.6, adjusted R^2 = 0.195, p value ≤0.001*				
Excluding former drinker	3,095	Unadjusted	2.05 (1.05–4.28)	0.043
		Adjusted	2.12 (1.08–4.44)	0.037
F statistics = 1,212, adjusted R^2 = 0.281, p value ≤0.001*				

Log-transformed alcohol consumption in men was estimated and inversely transformed according to whether the *ALDH2* rs671 genotype was GG or GA/AA.
All models were adjusted for age, physical activity, smoking status, body mass index category, hypertension, diabetes, and education status.
ALDH2 = aldehyde dehydrogenase 2; CI = confidence interval; OR = odds ratio.
*F statistics, adjusted R-squared, and p value of regression model which predicted log-transformed alcohol consumption using *ALDH2* genotype GG or GA/AA.

2.12 [95% CI, 1.08–4.44]). The F statistics and adjusted R^2 of MR model were 864.6 and 19.5% in total subjects and 1,212 and 28.1% in subjects except former drinkers.

DISCUSSION

We conducted an MR analysis to identify the causal association between alcohol consumption and AF. The relationship between alcohol consumption and AF seemed to be insignificant in the observational analysis. The MR analysis with genetically predicted alcohol consumption showed a causal association in men.

Previous studies identifying the link between alcohol consumption and AF using genetic factors presented conflicting results. In a Japanese study in 200 hospital inpatients, there was a significant difference in the distribution of *ALDH2* and *ADH1B* genotypes between patients with AF and patients with other diseases. Patients with AF have a lower frequency of the dysfunctional *ALDH2* allele and a higher frequency of the dysfunctional *ADH1B* allele, suggesting that higher alcohol consumption may be associated with AF. Unlike *ALDH2* variants, dysfunction of *ADH1B* slows the metabolism of alcohol to aldehyde, leading

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to increased alcohol consumption.[5] In addition, three previous MR studies examined the causal relationship between the amount of alcohol consumption and AF, which was unaffected by confounders. All studies were two-sample MR studies, and most of the study participants were of European ancestry. In the two-sample MR study performed by Jiang et al.,[16] genetically predicted alcohol consumption was not associated with AF. However, in the study by Larsson et al.,[17] genetically predicted alcohol consumption was positively associated with AF, and in the study by Lu et al.,[18] a positive relationship was found between genetically predicted heavy drinking (>35 units/week in women and >50 units/week in men) and AF.

In our study, a significant relationship between alcohol consumption and AF was observed only in the MR analysis in men. This discrepancy in results between the observational analysis and MR analysis may be caused by unknown confounding factors in the relationship between alcohol consumption and AF. In women, both the observational and genetic analyses did not present a significant relationship between alcohol consumption and AF. The sex differences in the distribution of alcohol consumption among rs671 genotypes led to the sex difference in the MR analysis results. In women, the amount of alcohol consumption was relatively lower than that in men because alcohol consumption is socially proscribed for women. Therefore, in women, physiologic discomfort due to ALDH dysfunction may not play a large role in determining the amount of alcohol consumption.[26]

In an MR analysis, several assumptions need to be satisfied for a variable to be used as a genetic instrument. First, the genetic variant is associated with the factor (relevance assumption). Second, there is no unknown confounder between genetic variants and outcome (independence assumption). Third, the genetic variants affect the outcome only through risk factors (exclusion restriction). If the relevance assumption is not met, a 'weak instrument problem' occurs, such as weak statistical power and increased bias due to pleiotropic effects. The relevance assumption is tested by checking whether the F statistic exceeds 10. The F value of the regression model for the alcohol consumption of the *ALDH2* genotype in this study is 864.6, so there is probably no violation of the relevance assumption. Independence assumption and exclusion restriction assumptions can be evaluated in "Negative control" populations which are rarely exposed to risk factors. These assumptions can be satisfied if IV is not associated with the outcome in these populations.[11] In the present study, alcohol consumption of women was close to zero, and there was no significant association between *ALDH2* polymorphism and AF in women. In addition, *ALDH2* was associated with AF after further adjustment for potential confounders or mediators which are the phenotypes known to be associated with the *ALDH2* rs671 genotype. Thus, the *ALDH2* polymorphism may be suitable IV on alcohol consumption in the present study. Furthermore, previous study reported *ALDH2* variants are the credible genetic IV for MR studies of alcohol consumption.[27]

Some limitations could be considered in this study. First, alcohol consumption may have not been accurately measured. In this study, the average daily alcohol consumption was calculated using the questionnaire responses of participants about the monthly drinking frequency and the amount of alcohol consumed at one time, and this value was used for all analyses. In the same context, former drinkers were treated as nondrinkers regardless of the amount of alcohol they had consumed in the past. To assess the bias in evaluating the relationship between alcohol consumption and AF due to the problem in the categorization of former drinkers, a sensitivity analysis was conducted including only current and never drinkers, in whom the effects of alcohol consumption could be clearly determined. Third, undiagnosed paroxysmal AF may have been missed and the prevalence may have been

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underestimated in the total participants. Clinically, AF can be classified into three categories: paroxysmal, persistent, and permanent. This classification depends on whether the AF is terminated spontaneously and how long the AF is sustained. The management and prognosis of AF can differ according to the classification.[28][29] To include patients with paroxysmal AF in our study, we included patients who had been diagnosed with AF, or were being treated for AF. Fourth, the MR results may be ethnic specific because *ALDH2* polymorphism exists only in East-Asian.[30]

In conclusion, genetically predicted alcohol consumption based on the rs671 polymorphism is associated with AF. This result suggests that the association between AF and alcohol consumption may be causal.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Association between alcohol consumption (drinks per day) and atrial fibrillation without former drinker in the observational analysis

Click here to view

Supplementary Table 2

Association between categorized alcohol consumption and atrial fibrillation in the observational analysis

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Supplementary Table 3

Association between rs671 polymorphisms and atrial fibrillation after further adjusting for *ALDH2* related phenotypes by sex

Click here to view

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