

Original Article
Preventive &
Social Medicine



OPEN ACCESS

Received: Nov 25, 2019

Accepted: Jan 6, 2020

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Effect Modification of Acetaldehyde Dehydrogenase 2 rs671 Polymorphism on the Association between Alcohol Intake and Blood Pressure: the Dong-gu Study

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ABSTRACT

Background: Elevated blood pressure is a major preventable cause of cardiovascular diseases. Alcohol consumption is a well-known risk factor of elevated blood pressure. The aldehyde dehydrogenase 2 (*ALDH2*) polymorphism is common in Eastern Asians, and inactive *ALDH2* genotypes are associated with both avoiding alcohol consumption and aldehyde accumulation. Therefore, this study assessed the associations between alcohol consumption and hypertension and blood pressure according to the *ALDH2* genotypes.

Methods: This study consists of 8,526 participants in the Dong-gu Study. Multivariate logistic regression was used to calculate the odds ratio (OR) according to alcohol consumption after stratifying by gender and *ALDH2* genotypes. Multivariate linear regression was performed to estimate the systolic blood pressure (SBP) and diastolic blood pressure (DBP) according to the amount of alcohol consumed.

Results: In men, alcohol consumption was positively associated with both SBP and DBP in active *ALDH2* carriers, but not in inactive *ALDH2* carriers. In active *ALDH2* carriers, compared to non-drinkers, the OR of hypertension was 1.16 (95% confidence interval [CI], 0.91–1.49) for < 1 drink/day, and 1.44 (95% CI, 1.15–1.80) for ≥ 1 drink/day in men. With each 1 drink/day increase, SBP and DBP increased by 3 and 1 mmHg in men, respectively. There was no significant association between *ALDH2* genotypes and hypertension and blood pressure in women.

Conclusion: *ALDH2* genotype modified the association between alcohol consumption and blood pressure in men. There was a positive relationship between alcohol consumption and blood pressure in active *ALDH2* carriers, but no significant relationship in inactive *ALDH2* carriers.

Keywords: ALDH2; Polymorphism; Hypertension; Cohort Studies

Funding

This study was supported by a grant from Chonnam National University Hospital Biomedical Research Institute (CRI18094-3).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

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

INTRODUCTION

Elevated blood pressure is a major preventable cause for cardiovascular diseases, including ischemic heart disease, stroke, heart failure, atrial fibrillation, and peripheral arterial disease, and a leading cause of all-cause mortality worldwide.¹ Lifestyle modification is important for the prevention and treatment of elevated blood pressure. This includes weight loss,² increased physical activity,³ and reduced alcohol consumption,⁴ which can reduce cardiovascular disease risk.

Alcohol is mainly metabolized by alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase. There are genetic differences in these enzymes in different ethnic groups. The aldehyde dehydrogenase 2 (*ALDH2*) variant is common in East Asians, and the activity of *ALDH2* varies by about 3–5 fold according to rs671,⁵ a missense *ALDH2* mutation. Mutations in *ALDH2* are closely related to the avoidance of alcohol drinking. Inactive *ALDH2* causes alcohol flush reactions such as erythema, nausea, and rapid heart rate as a result of aldehyde accumulation after alcohol consumption.^{6,7} Active *ALDH2* carriers who do not develop alcohol flushing tend to be drinkers with a greater amount of alcohol intake.⁸⁻¹⁰

Many previous studies have evaluated the association between the *ALDH2* rs671 polymorphism and blood pressure.^{9,11-16} In some studies,^{9,11,12,14,16} the *ALDH2* genotype was considered as an instrumental variable of alcohol consumption. However, the *ALDH2* genotype modifies the effects of alcohol via aldehyde accumulation. Therefore, it is necessary to evaluate the relationship between alcohol consumption and blood pressure through stratification analyses according to the *ALDH2* genotype. In this study, we evaluated the associations between alcohol consumption and blood pressure and hypertension after stratifying the *ALDH2* genotype.

METHODS**Study population**

This study was based on the Dong-gu Study, the framework of which has been described elsewhere.¹⁷ Briefly, the Dong-gu Study involved 9,260 participants aged ≥ 50 years who live in Gwangju, the metropolitan city in Korea. Of these, 495 participants with myocardial infarction or stroke were excluded. *ALDH2* genotyping was missing for 31 participants and information on alcohol consumption was missing for 131 participants. Ultimately, 8,526 participants without missing values were included in the analyses.

Blood pressure measurement and definition of hypertension

Blood pressure was measured by trained investigators three times at the right upper arm using a mercury sphygmomanometer after the participants had rested for ≥ 5 minutes. We used the mean of the three blood pressure measurements in the analyses. Hypertension was defined as either systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or taking antihypertensive medication.

Assessment of lifestyles and comorbidities

Information on variables such as lifestyle and disease history was obtained through interview questionnaires. The frequency and amount per occasion of alcohol consumption were investigated; a non-drinker was defined as a participant who consumed less than one drink

per month. Alcohol consumption was coded as non-drinker, less than one standard drink per day, or one or more standard drinks per day. Smoking status was coded as never, ex-smoker, or current smoker. Physical activity was coded as walking for at least 30 minutes on at least 5 days per week or not. Body mass index (BMI) was calculated in kilograms per meter squared from weight and height measured in a standing position without shoes. A history of diabetes was assessed using questionnaires.

Genotyping

Genomic DNA was extracted from peripheral blood using a QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA, USA), according to the manufacturer's protocol. rs671 was genotyped by high-resolution melting (HRM) analyses, using a Rotor-Gene 6000TM (Corbett Research, Sydney, Australia). The forward primer (5'-TTGGTGGCTACAAGATGTCG-3') and reverse primer (5'-CAGGTCCCACACTCACAGTTT-3') polymerase chain reaction (PCR) primers producing a 97-bp amplicon. The reaction mixture for HRM included 200 nM PCR primers, 1 μ M SYTO 9 fluorescent dye (Invitrogen, Carlsbad, CA, USA), 0.5U F-Star *Taq* DNA polymerase (BioFACT), and 40 ng genomic DNA in 10 μ L reaction volumes. The cycling conditions comprised an initial denaturation at 95°C for 5 minutes, followed by 40 cycles of 95°C for 5 seconds and 58°C for 30 seconds.

Statistical analysis

The baseline characteristics of the study population are presented according to gender and *ALDH2* genotype. General characteristics are expressed as means \pm standard deviations or number (%). The general characteristics of the participants were compared using *t*-tests for continuous variables, and χ^2 tests for categorical data. Genotype was categorized as active *ALDH2* (GG) and inactive *ALDH2* (GA/AA). All analyses were carried out by gender. Multivariate linear regression was performed to assess the associations between *ALDH2* and alcohol consumption and SBP and DBP. Multivariate logistic regression was performed to assess the associations between *ALDH2* genotypes and alcohol consumption and hypertension.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Chonnam National University Hospital (IRB No. I-2008-05-056), and informed consent was obtained from each subject.

RESULTS

Table 1 shows the baseline characteristics according to the *ALDH2* genotype and gender. The GG, GA, and AA genotype frequencies were 69.0%, 28.4%, and 2.6%, respectively, and were in Hardy–Weinberg equilibrium ($P = 0.141$). Inactive *ALDH2* carriers were significantly older and had a lower alcohol consumption and lower DBP than active *ALDH2* carriers in both genders. They had a lower BMI and SBP and a higher prevalence of hypertension, and diabetes only in men.

Table 2 shows the odds ratios (ORs) for hypertension in participants who were inactive *ALDH2* carriers compared to active *ALDH2* carriers. In the crude model, the ORs in men and women were 1.27 (95% confidence interval [CI], 1.10–1.47) and 1.04 (95% CI, 0.92–1.17), respectively. After adjusting for age, the risk difference was greater in model 1, and the ORs were 1.34 (95% CI, 1.16–1.56) in men and 1.09 (95% CI, 0.96–1.23) in women. In the final model, the ORs were 1.24 (95% CI, 1.06–1.45) in men and 1.08 (95% CI, 0.95–1.22) in women.

Table 1. General characteristics of study subjects according to genotype of *ALDH2* rs671

Characteristics	Men			Women		
	GG	GA/AA	P value	GG	GA/AA	P value
Total	2,242 (67.6)	1,077 (32.4)		3,638 (69.9)	1,569 (30.1)	
Age, yr	65.6 ± 8.0	67.0 ± 7.9	< 0.001	64.1 ± 8.1	64.8 ± 8.3	0.005
Smoking status			0.569			0.020
Never smoker	570 (25.4)	283 (26.3)		3,491 (96.0)	1,530 (97.5)	
Ex-smoker	1,116 (49.8)	515 (47.8)		67 (1.8)	19 (1.2)	
Current smoker	556 (24.8)	279 (25.9)		80 (2.2)	20 (1.3)	
Physical activity	601 (26.8)	272 (25.3)	0.342	465 (12.8)	202 (12.9)	0.927
Alcohol consumption, drink/day			< 0.001			< 0.001
Non-drinker	535 (23.9)	686 (63.7)		2,789 (76.7)	1,475 (94.0)	
< 1	589 (26.3)	271 (25.2)		716 (19.7)	85 (5.4)	
≥ 1	1,118 (49.9)	120 (11.1)		133 (3.7)	9 (0.6)	
Drinks/day	2.0 (2.6)	0.4 (1.1)	< 0.001	0.1 (0.5)	0.0 (0.2)	< 0.001
Hypertension	1,048 (46.7)	440 (40.9)	0.001	1,559 (42.9)	657 (41.9)	0.512
Diabetes	576 (25.7)	184 (17.1)	< 0.001	563 (15.5)	238 (15.2)	0.778
BMI, kg/m ²	24.0 ± 2.8	23.6 ± 2.8	< 0.001	24.6 ± 3.0	24.6 ± 2.9	0.399
SBP, mmHg	125.6 ± 16.4	122.5 ± 16.8	< 0.001	122.4 (17.0)	122.0 (16.7)	0.451
DBP, mmHg	76.0 ± 10.6	74.6 ± 10.5	< 0.001	73.8 (9.9)	72.9 (9.8)	0.003

All values are given as mean ± standard deviation or number (%).

ALDH2 = aldehyde dehydrogenase 2, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table 2. Association between *ALDH2* rs671 polymorphism and HTN according to gender

Variables	HTN (-)	HTN (+)	Crude model	Model 1	Model 2	P for interaction ^a
Men						
GG	1,194 (65.2)	1,048 (70.4)	1.27 (1.10–1.47)	1.34 (1.16–1.56)	1.24 (1.06–1.45)	
GA/AA	637 (34.8)	440 (29.6)	1 (Ref.)	1 (Ref.)	1 (Ref.)	
Women						
GG	2,079 (69.5)	1,559 (70.4)	1.04 (0.92–1.17)	1.09 (0.96–1.23)	1.08 (0.95–1.22)	
GA/AA	912 (30.5)	657 (29.7)	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.116

All values are given as odds ratio (95% confidence interval) or number (%).

Model 1 was adjusted for age. Model 2 was further adjusted for smoking, physical activity, diabetes mellitus, and body mass index.

ALDH2 = aldehyde dehydrogenase 2, HTN = hypertension.

^aP value for interaction term between gender and *ALDH2* rs671 genotype in model 2.

Table 3 shows the SBP and DBP according to *ALDH2* genotypes and gender. The association between SBP and *ALDH2* genotype was modified by gender (*P* for interaction = 0.002). In men, inactive *ALDH2* carriers had a lower SBP and DBP, while in women, SBP did not differ significantly according to *ALDH2* genotype, and inactive *ALDH2* carriers genotype had a lower DBP.

Table 3. Association between *ALDH2* rs671 polymorphism and blood pressure according to gender

Variables	SBP			DBP		
	Crude	Model 1	Model 2	Crude	Model 1	Model 2
Men						
GG	125.6 ± 0.4	125.7 ± 0.3	125.6 ± 0.4	76.0 ± 0.2	76.0 ± 0.2	76.0 ± 0.2
GA/AA	122.5 ± 0.5	122.2 ± 0.5	122.5 ± 0.5	74.6 ± 0.3	74.6 ± 0.3	74.6 ± 0.3
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Women						
GG	122.4 ± 0.3	122.5 ± 0.3	122.4 ± 0.3	73.8 ± 0.2	73.8 ± 0.2	73.8 ± 0.2
GA/AA	122.0 ± 0.4	121.8 ± 0.4	121.8 ± 0.4	72.9 ± 0.3	73.0 ± 0.3	73.0 ± 0.3
P value	0.451	0.155	0.196	0.003	0.007	0.009
P for interaction ^a			0.002			0.537

Values are given as adjusted mean ± standard error.

Model 1 was adjusted for age. Model 2 was further adjusted for smoking, physical activity, diabetes mellitus, and body mass index.

ALDH2 = aldehyde dehydrogenase 2, SBP = systolic blood pressure, DBP = diastolic blood pressure.

^aP value for interaction term between gender and *ALDH2* rs671 genotype in model 2.

Table 4 shows the association between alcohol consumption and the risk of hypertension according to *ALDH2* genotypes and gender. The association between alcohol consumption and risk of hypertension was only significant in men who had the active *ALDH2* genotype, while not significant in women.

Table 5 shows the dose-response relationship between alcohol consumption and blood pressure for each *ALDH2* genotype. The *ALDH2* genotype modified the association between alcohol consumption and SBP (*P* for interaction < 0.001) and DBP (*P* for interaction = 0.007) in men, but not in women. The association between alcohol consumption and blood pressure was not significant in women, while in men, both SBP and DBP increased with alcohol consumption in the active *ALDH2* carrier. By contrast, the inactive *ALDH2* carrier was not related to alcohol consumption or blood pressure.

Table 4. Association between alcohol consumption and HTN, stratified by gender and *ALDH2* rs671 genotype

Variables	Men			Women		
	HTN (-)	HTN (+)	OR (95% CI)	HTN (-)	HTN (+)	OR (95% CI)
GG genotype						
Non-drinker	304 (56.8)	231 (43.2)	1 (Ref.)	1,573 (56.4)	1,216 (43.6)	1 (Ref.)
Current drinker, drink/day	890 (52.1)	817 (47.9)	1.33 (1.08-1.64)	506 (59.6)	343 (40.4)	1.05 (0.89-1.24)
< 1	316 (53.7)	273 (46.3)	1.16 (0.91-1.49)	434 (60.6)	282 (39.4)	1.00 (0.84-1.20)
≥ 1	574 (51.3)	544 (48.7)	1.44 (1.15-1.80)	72 (54.1)	61 (45.9)	1.30 (0.90-1.87)
<i>P</i> value for trend ^a			0.001			0.344
GA/AA genotype						
Non-drinker	404 (58.9)	282 (41.1)	1 (Ref.)	851 (57.7)	624 (42.3)	1 (Ref.)
Current drinker, drink/day	233 (59.6)	158 (40.4)	1.12 (0.85-1.46)	61 (64.9)	33 (35.1)	1.02 (0.64-1.63)
< 1	163 (60.1)	108 (39.9)	1.05 (0.77-1.42)	55 (64.7)	30 (35.3)	1.00 (0.61-1.64)
≥ 1	70 (58.3)	50 (41.7)	1.29 (0.85-1.96)	6 (66.7)	3 (33.3)	1.25 (0.28-5.55)
<i>P</i> value for trend ^a			0.279			0.874
<i>P</i> for interaction ^b			0.247			0.791

All models were adjusted for age, smoking history, physical activity, diabetes mellitus, and body mass index.

ALDH2 = aldehyde dehydrogenase 2, HTN = hypertension, OR = odds ratio, CI = confidence interval.

^aTrend test from non-drinker, < 1 drink/day, to ≥ 1 drink/day; ^b*P* value for interaction term between alcohol consumption (non-drinker and current drinker) and *ALDH2* rs671 genotype.

Table 5. Association between alcohol consumption and blood pressure, stratified by *ALDH2* rs671 genotype

Variables	Men			Women		
	No.	SBP, mmHg	DBP, mmHg	No.	SBP, mmHg	DBP, mmHg
GG genotype						
Non-drinker	535 (23.9)	121.9 ± 0.7	74.3 ± 0.4	2,789 (76.7)	122.3 ± 0.3	73.7 ± 0.2
Current drinker, drink/day	1,707 (76.1)	126.7 ± 0.4	76.5 ± 0.2	849 (23.3)	122.6 ± 0.6	74.2 ± 0.3
< 1	589 (26.3)	125.1 ± 0.7	75.6 ± 0.4	716 (19.7)	122.2 ± 0.6	74.0 ± 0.4
≥ 1	1,118 (49.9)	127.6 ± 0.5	77.1 ± 0.3	133 (3.7)	124.3 ± 1.4	75.0 ± 0.8
<i>P</i> value for trend ^a		< 0.001	< 0.001		0.414	0.146
GA/AA genotype						
Non-drinker	686 (63.7)	122.6 ± 0.6	74.4 ± 0.4	1,475 (94.0)	121.8 ± 0.4	72.9 ± 0.2
Current drinker, drink/day	391 (36.3)	122.4 ± 0.8	74.8 ± 0.5	94 (6.0)	125.1 ± 1.7	74.2 ± 1.0
< 1	271 (25.2)	122.3 ± 1	74.6 ± 0.6	85 (5.4)	125.0 ± 1.8	74.3 ± 1.1
≥ 1	120 (11.1)	122.7 ± 1.5	75.1 ± 0.9	9 (0.6)	126.2 ± 5.4	72.9 ± 3.2
<i>P</i> value for trend ^a		0.954	0.530		0.055	0.269
<i>P</i> for interaction ^b		< 0.001	0.007		0.112	0.488

Values are adjusted mean ± standard error after adjusting for age, smoking history, physical activity, diabetes mellitus, and body mass index.

ALDH2 = aldehyde dehydrogenase 2, SBP = systolic blood pressure, DBP = diastolic blood pressure.

^aTrend test from non-drinker, < 1 drink/day, to ≥ 1 drink/day; ^b*P* value for interaction term between alcohol consumption (non-drinker and current drinker) and *ALDH2* rs671 genotype.

DISCUSSION

In this study, active *ALDH2* carriers were associated with a high risk of hypertension in men. The association between alcohol consumption and SBP was dose-dependent in active *ALDH2* carriers. However, there was no significant association between the *ALDH2* polymorphism and hypertension and blood pressure in women.

In previous studies, active *ALDH2* carriers had a higher risk for hypertension than inactive *ALDH2* carriers.^{9,11-13,16} The difference in blood pressure according to the activity of *ALDH2* can be explained by the difference in alcohol consumption. In previous studies, active *ALDH2* carriers included a high prevalence of drinkers or greater alcohol consumption.⁸⁻¹⁰ In our study, compared to inactive *ALDH2* carriers, active *ALDH2* carriers have 1.7 more drinks per day in men. In women, however, the amount of alcohol consumption was so small that the difference in consumption by the *ALDH2* genotype was not significant.¹⁶ By contrast, Zhang et al.¹⁴ found no significant association between *ALDH2* genotype and blood pressure in both never and current drinkers. In their study, there was an overadjustment bias due to the unnecessary adjustment of the frequency of alcohol consumption, an intermediate variable, in the association between *ALDH2* genotype and blood pressure.¹⁸ In our study, active *ALDH2* carriers had a 3.1 mmHg higher SBP and 1.4 mmHg higher DBP than inactive *ALDH2* carriers in men. Ota et al.¹⁵ reported a 3.3 mmHg higher SBP and 2.6 mmHg higher DBP in active *ALDH2* carriers compared to inactive *ALDH2* carriers. In the study of Isomura et al.,¹² the SBP and DBP of active *ALDH2* carriers were 1.8 and 1.3 mmHg higher than those of inactive *ALDH2* carriers, respectively. We also found a dose-response relationship between alcohol consumption and blood pressure in active *ALDH2* carriers. Similarly, meta-analysis studies of observational studies and clinical trials found a positive dose-response relationship between the amount of alcohol consumption and incidence of hypertension,¹⁹ and reducing alcohol consumption led to lower blood pressure.⁴ Chronic alcohol consumption increases blood pressure via increased sympathetic nerve activity, reduced antioxidants, and impaired vascular relaxation.²⁰

In our study, the *ALDH2* genotype modified the association between alcohol consumption and blood pressure. There were dose-response relationships between alcohol consumption and SBP and DBP in active *ALDH2* carriers, but no significant relationship in inactive *ALDH2* carriers. In inactive *ALDH2* carriers, it is not clear why blood pressure did not increase with the amount of alcohol consumption. Based on our results, we postulate that other blood pressure lowering effects of ethanol metabolites, such as aldehyde, counteract the ethanol-induced blood pressure increase. After alcohol consumption, inactive *ALDH2* carriers have a fivefold higher peak blood aldehyde level than active *ALDH2* carriers. Aldehyde lowers blood pressure in the early phase after drinking alcohol. In an animal study, an inactive *ALDH2*-like disulfiram-treated group had a lower blood pressure than a control group after ethanol administration.²¹ Few studies have evaluated the dose-response relationship between alcohol consumption and blood pressure according to the *ALDH2* genotype. In contrast with our results, Ota et al.¹⁵ reported a significant positive association between the amount of alcohol consumption and SBP only in inactive *ALDH2* carriers. However, their study population was small and consisted of only men workers with high alcohol consumption.

In inactive *ALDH2* carriers, the difference in the amount of alcohol consumption among categories of alcohol consumption was not sufficiently large, so the association between alcohol consumption and blood pressure may not have been evaluated sufficiently. Drinkers

who are inactive *ALDH2* carriers consume less alcohol than drinkers who are active *ALDH2* carriers.¹⁰ Because the difference in alcohol consumption between drinkers and non-drinkers in the inactive *ALDH2* carrier is less than that of the active *ALDH2* carrier, the effects of drinking on the increase in blood pressure were weak in inactive *ALDH2* carriers. In our study, of those who drank more than one drink per day, those with the inactive *ALDH2* genotype drank 2.88 drinks per day, whereas those with the active *ALDH2* genotype had 3.89 drinks per day. The binge-drinking rate was 64.5% in the drinkers with the active *ALDH2* genotype, but 28.5% in those with the inactive genotype (data not shown).

The main strength of our study was the large sample size, which enabled us to evaluate the association between alcohol consumption and blood pressure according to *ALDH2* genotypes. The limitation of our study is that other polymorphisms affecting alcohol metabolism, such as ADH 1B (*ADH1B*), were not evaluated in this study. However, *ADH1B* polymorphism was not significantly associated with a high risk of hypertension¹³ or high blood pressure¹⁴ in previous studies.

In conclusion, there was a positive dose-response relationship between alcohol consumption and blood pressure in active, but not in inactive, *ALDH2* carriers. Further studies are needed to clarify the mechanism of effect modification of the *ALDH2* rs671 polymorphism on the association between alcohol intake and blood pressure.

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