The Alcohol Flushing Response is Associated with the Risk of Depression

Seonghee Jeon
Seoul National University
Heewon Kang
Seoul National University
Inhyung Cho
Seoul National University
Sung-il Cho (persontime@hotmail.com)
Seoul National University

Research Article

Keywords: alcohol flushing response, risk, depression, East Asians, major health problem, population

Posted Date: December 10th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1095598/v1

Abstract

The alcohol flushing response is experienced by 36–45% of East Asians after drinking a small amount of alcohol. Since individuals with this response are incapable of metabolizing toxic acetaldehyde derived from alcohol effectively, this response is suggested as an indicator for the health risks associated with alcohol intake. Depression, a major health problem linked to alcohol consumption, might also be associated with the presence of the alcohol flushing response. Therefore, this study examined the association between the alcohol flushing response and the risk of depression in the general population of South Koreans. The analysis included 139,266 participants and used data from the 2019 Korean Community Health Survey. Only current drinkers were considered in the analysis. The relationship between the alcohol flushing response and depression was determined by logistic regression analysis using SAS 9.4. As a result, more than one-third of the population was found to be current flushers, and the relationship was significant among current flushers and depression (AOR=1.23, 95% CI 1.12–1.35, P-value=0.1×10-3) compared to never flushers. No association was found between former flushing response and depression. The odds of depression were significantly higher among alcohol flushers who drinks less than 15 g/day alcohol (<5 g/day: AOR=1.21, 95% CI=1.08-1.36, P-value=0.1×10-3; 5.0-14.9 g/day: AOR=1.40, 95% CI=1.14-1.71, P-value=0.1×10-3). In conclusion, this study reveals that a significant number of the South Korean population experiences the alcohol flushing response, and the individuals with the response are more likely to feel depressed, even with a small amount of alcohol consumption.

Introduction

The alcohol flushing response, which is observed in 36–45% of East Asians (Koreans, Chinese, and Japanese)[1,2], occurs in carriers of mutant ALDH2*2 alleles that render ALDH2 inactive. Since ALDH2 encodes the enzyme that eliminates toxic acetaldehyde derived from alcohol, individuals with inactive ALDH2 metabolize acetaldehyde slower or not at all[3]. ALDH2*2/*2 homozygotes lack detectable ALDH2 activity, while heterozygotes (ALDH2*1/*2) have 100-fold reduced ALDH2 activity. Consequently, there is a significant increase in the blood acetaldehyde concentration after drinking alcohol[4]. Even after consuming a small amount of alcohol, excess acetaldehyde accumulates and leads to a physiological response called the alcohol flushing response that involves facial flushing[1]. These people are not protected from the risks of alcohol intake because they are incapable of metabolizing acetaldehyde effectively.

Depression is a major health problem associated with alcohol consumption. Acetaldehyde may contribute to anxious or depressive states via bidirectional effects on corticotropin-releasing hormone and neuropeptide Y, two major stress-related peptides with functionally opposite effects[5]. The interaction between acetaldehyde and dopamine leads to the development of addictive behavior, which is highly relevant to alcohol-use disorders (AUDs), which may accompany mental disorders such as depression[5]. An AUD doubles the risks of major depression[6].

Due to the adverse reactions that alcohol flushing individuals (flushers) experience after drinking, they drink less than non-flushers[7]. Therefore, some propose that individuals with inactive ALDH2 are less likely to develop AUD[8]. Nonetheless, as flushers are more vulnerable to the adverse effects of acetaldehyde, they might experience AUD-induced depression despite drinking less than non-flushers. They might also experience depression induced by heavy drinking[9], which is often followed by alcohol withdrawal symptoms, which are associated with decreased blood serotonin levels and depression[10].

A study showed that ALDH2*1/*2 individuals have the highest odds of depression compared with other groups with lower sensitivity to alcohol[11]. However, there is still no solid evidence of a connection between depression and the flushing response or inactive ALDH2, with relatively few published studies on the subject. Therefore, we sought to clarify the association between the alcohol flushing response and depression in a large sample from the South Korean general population.

Methods

Study population

The study used data from the 2019 Korean Community Health Survey, a community-based, cross-sectional survey directed by the Korea Disease Control and Prevention Agency. The survey provides data to be used in planning, implementing, monitoring, and evaluating community health promotion and programs for disease prevention. The major subjects covered in this survey are personal health practices and behaviors associated with diseases, such as smoking, alcohol use, and physical activities. The informed consent was obtained from all participants.

Of the 229,099 participants who completed the 2019 Korean Community Health Survey, 82,767 were non-drinkers, and 7,066 had missing values regarding the grade of depression, alcohol flushing status, and other covariates. The final study population comprised 139,266 current drinkers.

This study was exempt from IRB review by the Institutional Review Board of Seoul National University (IRB Number: E2106/002-002), and was held according to the relevant guidelines and regulations.

Measures

The presence of depression was identified via the Patient Health Questionnaire 9 (PHQ-9), a simple measure that aligns with the DSM-IV criteria[15]. The frequency of depression-related symptoms is rated based on the respondents' experience over the past 2 weeks, using a four-point scale (from not at all to nearly every day). The scores are summed as the index of depressive symptoms, with a maximum possible score of 27. A score > 10 was defined as having depression.

The presence of an alcohol flushing response was identified by the questions: (a) Do you have a tendency to flush in the face immediately after drinking as little as a glass of beer (no, occasionally, often, or always)? (b) Did you have a tendency to flush in the face immediately after drinking as little as a glass

of beer during the first to second year you started drinking (yes or no)? Respondents who answered ‘occasionally’, ‘often’, or ‘always’ to question (a) were classified as ‘current flushers’. Those who answered ‘no’ to question (a), but ‘yes’ to question (b) were classified as ‘former flushers’, and those who answered ‘no’ to both questions were classified as ‘never flushers’. These questions have a 95.1% sensitivity and 76.5% specificity for detecting inactive ALDH2 among Koreans[16].

Alcohol intake as grams of alcohol consumed per day (g/day) was obtained by graduated frequency (GF) measure[17]. We calculated the product of the frequency of drinking occasions (abstainers, less than 1 time a month, about 1 time a month, 2-4 times a month, 2-3 times a week, and more than 4 times a week) and the usual number of drinks consumed per occasion (1-2, 3-4, 5-6, 7-9, and 10+ drinks), and converted the scale from drinks to grams of alcohol (7 grams per one standard drink in Korea)[18]. The values used for quantities were the arithmetic mid-points of the number of drinks consumed per occasion (approximate mid-points): 0, 6, 12, 36, 120, and 264. Thus, the alcohol intake was classified into four categories: <5 g/day, 5-14.9 g/day, 15-29.9 g/day, and above 30 g/day.

Basic characteristics and variables that show association with depression were set as covariates for the analysis. Respondents’ sex, age, family income level, educational level, smoking status, obesity status, exercise, and social activity was considered as either possible intermediates or potential confounders in this study.

Age was categorized into 19 to 39 years, 40 to 59 years, 60 to 69 years, and 70 years or above, for even distribution between the age groups. Obesity status was categorized as yes or no (BMI≥25.0 kg/m^2 or BMI<25.0 kg/m^2) according to Asian-Pacific cutoff points[19]. Smoking status was grouped as never smoker, ex-smoker, and current smoker. Exercise was categorized as yes or no according to the participants’ past exercising status (either they have engaged in vigorous intensity physical activity for more than 20 minutes for more than 3 days per week or have engaged in moderate intensity physical activities for more than 30 minutes for more than 5 days per week over the past week). Social activity was categorized as yes or no. The participants who participate in more than one of the following social activities were classified as yes: religion, friendship, leisure, or charity. Educational level was categorized as none, primary education, secondary education, tertiary education. Income level was categorized into four quantiles. Occupation status was categorized as managers or professional, clerical workers, service and sales workers, agricultural, forestry and fishery workers, technicians and operators, house-wife, unemployed, and others. Hypertension and diabetes mellitus were classified as yes or no according to the past experience of being diagnosed with the diseases or not.

Statistical analyses

Non-weighted frequencies and weighted percentages were calculated for the descriptive characteristics of the study respondents. Chi-square statistics were used to examine the statistical significance of distinction in depression. Logistic regression analysis was used to evaluate the association between alcohol flushing and depression, adjusting for sex, age, obesity, smoking status, exercise status, social

activity, family income level, education level, occupation, alcohol intake, drinking initiation age, attempts to cut down/quit drinking, hypertension, and diabetes mellitus. In this analysis, the alcohol flushing response was set as independent variable, and the presence of depressive symptoms (depression) was set as dependent variable. This relationship was then investigated by different range of alcohol intake amount (less than 5 g/day, 5-14.9 g/day, 15-29.9 g/day, and above 30 g/day) with the adjustment of confounding variables. All the analyses were conducted using SAS ver. 9.4 (SAS Institute, Cary, NC, USA). Two-sided *p*-values were used, and the level of statistical significance was set at < 0.05.

Results

Characteristics according to the alcohol flushing status. Among the study participants, 61.1% were never flushers, 34.8% were current flushers, and 4.1% were former flushers. Regardless of the flushing status, the proportion of male, age 40–59 years, not obese, never smokers, not engaging in physical activity, engaging in social activity, 4th quartile family income level, technician or operator, and people without hypertension or diabetes mellitus were higher. Approximately 90% of the study participants received secondary to tertiary education.

While the proportions of current flushers were concentrated on people who drink monthly or less and who drink 1-2 drinks per occasion, the proportion of never and former flushers were concentrated on who drink 2–4 times per month. Correspondingly, more than 70% of the current flushers drink less than 5 g/day alcohol. The drinking initiation age of participants was generally above 19 years, and less than one-fifth (14.2%) had attempted to cut down or quit drinking (Table 1).

Table 1

Characteristics of the participants according to alcohol flushing status (n = 139,266). Descriptive data are unweighted frequencies (n) with weighted percentages (%). 1 drink = 7 g alcohol. Abbreviations: BMI, body mass index (kg/m2).

n (%)	Total	Never flusher	Former flusher	Current flusher	*p*-value
Total	139,266 (100.0)	84,235 (61.1)	6,106 (4.1)	48,925 (34.8)	<0.001
Sex					
Male	73,787 (55.9)	44,196 (55.7)	3,481 (58.6)	26,110 (55.8)	0.002
Female	65,479 (44.1)	40,039 (44.3)	2,625 (41.4)	22,815 (44.2)	
Age (years)					
19–39	39,497 (39.3)	25,333 (41.2)	1,135 (28.1)	13,029 (37.4)	<0.001
40–59	57,441 (42.6)	34,920 (42.3)	2,656 (47.9)	19,865 (42.6)	
60–69	24,365 (11.2)	13,766 (10.3)	1,350 (15.2)	9,249 (12.3)	
70+	17,963 (6.8)	10,216 (6.2)	965 (8.7)	6,782 (7.7)	
Obesity status					
No (BMI <25.0)	88,723 (64.6)	53,953 (64.8)	3,792 (63.1)	30,978 (64.6)	0.118
Yes (BMI ≥25.0)	50,543 (35.4)	30,282 (35.2)	2,314 (36.9)	17,947 (35.4)	
Smoking status					
Never smoker	80,586 (57.8)	49,425 (58.5)	3,167 (52.3)	27,994 (57.1)	<0.001
Ex-smoker	29,269 (19.8)	16,505 (18.7)	1,549 (23.3)	11,215 (21.4)	
Current smoker	29,411 (22.4)	18,305 (22.8)	1,390 (24.4)	9,716 (21.5)	
Exercise					
No	103,268 (74.3)	62,622 (74.3)	4,465 (74.0)	36,181 (74.3)	0.886

n (%)	Total	Never flusher	Former flusher	Current flusher	*p*-value
Yes	35,998 (25.7)	21,613 (25.7)	1,641 (26.0)	12,744 (25.7)	
Social activity					
No	37,749 (28.7)	23,339 (29.5)	1,615 (27.4)	12,795 (27.6)	<0.001
Yes	101,517 (71.3)	60,896 (70.5)	4,491 (72.6)	36,130 (72.4)	
Family income level					
1st quartile	31,010 (14.4)	17,885 (13.7)	1,621 (17.1)	11,504 (15.3)	<0.001
2nd quartile	20,696 (12.8)	12,256 (12.5)	967 (13.7)	7,473 (13.2)	
3rd quartile	39,519 (29.9)	23,965 (29.7)	1,633 (29.5)	13,921 (30.3)	
4th quartile	48,041 (42.9)	30,129 (44.0)	1,885 (39.7)	16,027 (41.2)	
Education level					
None	6,293 (1.8)	3,781 (1.7)	345 (2.4)	2,167 (1.8)	<0.001
Primary	14,542 (5.3)	8,131 (4.9)	841 (7.8)	5,570 (5.8)	
Secondary	66,149 (45.9)	39,336 (45.0)	3,110 (51.3)	23,703 (47.0)	
Tertiary	52,282 (47.0)	32,987 (48.5)	1,810 (38.6)	17,485 (45.4)	
Occupation					
Manager/professional	17,530 (16.2)	11,078 (16.9)	599 (13.2)	5,853 (15.5)	<0.001
Clerical	15,895 (14.5)	9,996 (14.9)	548 (12.5)	5,351 (14.0)	
Service/sales	21,034 (15.5)	12,712 (15.3)	900 (15.4)	7,422 (15.8)	
Agricultural/forestry/fishery	13,475 (2.7)	7,690 (2.5)	748 (3.6)	5,037 (2.8)	
Technician/operator	30,092 (21.5)	17,800 (20.9)	1,559 (26.7)	10,733 (21.9)	
Housewife	19,151 (13.1)	11,647 (13.0)	792 (13.6)	6,712 (13.4)	

n (%)	Total	Never flusher	Former flusher	Current flusher	*p*-value
Unemployed	16,376 (10.5)	9,537 (10.0)	827 (11.4)	6,012 (11.2)	
Others	5,713 (6.1)	3,775 (6.6)	133 (3.6)	1,805 (5.5)	
Drinking frequency					
Monthly or less	52,273 (36.5)	27,423 (31.0)	1,781 (27.7)	23,069 (47.2)	<0.001
2–4 times per month	42,063 (32.7)	26,407 (34.1)	1,763 (32.6)	13,893 (30.3)	
2–3 times per week	29,599 (22.0)	20,132 (25.0)	1,498 (25.5)	7,969 (16.3)	
4+ times per week	15,331 (8.8)	10,273 (9.9)	1,064 (14.2)	3,994 (6.3)	
Drinks per occasion					
1–2	50,277 (32.5)	26,355 (27.2)	1,901 (26.9)	22,021 (42.5)	<0.001
3–4	29,790 (21.1)	17,394 (20.1)	1,373 (22.4)	11,023 (22.7)	
5–6	17,459 (13.3)	11,237 (14.0)	783 (13.9)	5,439 (12.0)	
7–9	23,218 (17.8)	15,873 (20.2)	1,156 (20.1)	6,189 (13.1)	
10+	18,522 (15.3)	13,376 (18.4)	893 (16.7)	4,253 (9.6)	
Alcohol intake (g/day)					
<5.0	84,815 (60.0)	46,835 (54.1)	3,160 (51.0)	34,820 (71.5)	<0.001
5.0–14.9	26,840 (20.5)	18,057 (23.1)	1,331 (23.4)	7,452 (15.8)	
15.0–29.9	17,510 (13.1)	12,338 (15.5)	946 (15.7)	4,226 (8.6)	
30+	10,101 (6.3)	7,005 (7.3)	669 (9.9)	2,427 (4.1)	
Drinking initiation age					
<19	36,460 (28.3)	22,436 (28.6)	1,743 (30.2)	12,281 (27.6)	<0.001

n (%)	Total	Never flusher	Former flusher	Current flusher	*p*-value
19+	102,806 (71.7)	61,799 (71.4)	4,363 (69.8)	36,644 (72.4)	
Attempt to cut down/quit drinking					
No	119,447 (85.8)	71,897 (85.0)	4,838 (79.1)	42,712 (87.9)	<0.001
Yes	19,819 (14.2)	12,338 (15.0)	1,268 (20.9)	6,213 (12.1)	
Hypertension					
No	107,678 (83.3)	65,563 (83.6)	4,373 (78.0)	37,742 (83.2)	<0.001
Yes	31,588 (16.7)	18,672 (16.4)	1,733 (22.0)	11,183 (16.8)	
Diabetes mellitus					
No	127,324 (93.6)	77,498 (94.0)	5,477 (91.6)	44,349 (93.1)	<0.001
Yes	11,942 (6.4)	6,737 (6.0)	629 (8.4)	4,576 (6.9)	

Alcohol flushing response and depression. The prevalence of depression was highest among current flushers (weighted prevalence 2.92%, 2.63%, and 2.51% for current, former, and never flushers, respectively). The adjusted odds of depression were significantly higher among current flushers than never flushers (adjusted odds ratio 1.23, 95% CI 1.12–1.35, P-value=0.1×10^{-3}). Adjusted confounders were sex, age, obesity, smoking status, exercise status, social activity, family income level, education level, occupation, alcohol intake, drinking initiation age, attempt to cut down or quit drinking, hypertension and diabetes mellitus (Table 2).

Table 2

Association between the alcohol flushing response and depression. †OR were adjusted for sex, age, obesity, smoking status, exercise, social activity, family income level, education level, occupation, alcohol intake, drinking initiation age, attempt to cut down/quit drinking, hypertension, and diabetes mellitus. Abbreviations: AOR, adjusted odds ratio; BMI, body mass index (kg/m2); CI, confidence interval; Ref, reference.

	No depression/depression	Weighted prevalence (%)	AOR (95% CI)†	*P-value*
Alcohol flushing status				
Never	82,244/1,991	2.51	1 (Ref.)	
Former	5,946/160	2.63	1.01 (0.82-1.24)	0.9384
Current	47,621/1,304	2.92	1.23 (1.12-1.35)	<.0001
Sex				
Male	72,502/1,285	1.87	1 (Ref.)	
Female	63,309/2,170	3.67	3.13 (2.72-3.59)	<.0001
Age (years)				
19–39	38,228/1,269	3.39	1 (Ref.)	
40–59	56,339/1,102	1.95	0.60 (0.54-0.67)	<.0001
60–69	23,866/499	2.28	0.48 (0.40-0.57)	<.0001
70+	17,378/585	3.46	0.49 (0.39-0.60)	<.0001
Obesity status				
No (BMI <25.0)	86,457/2,266	2.71	1 (Ref.)	
Yes (BMI ≥25.0)	49,354/1,189	2.58	1.05 (0.96-1.16)	0.2909
Smoking status				
Never smoker	78,548/2,038	2.71	1 (Ref.)	
Ex-smoker	28,757/512	1.81	1.12 (0.96-1.32)	0.151
Current smoker	28,506/905	3.29	1.75 (1.53-2.01)	<.0001
Exercise				

	No depression/depression	Weighted prevalence (%)	AOR (95% CI)†	*P-value*
No	100,562/2,706	2.78	1 (Ref.)	
Yes	35,249/749	2.30	0.98 (0.88-1.09)	0.6806
Social activity				
No	36,195/1,554	4.32	1 (Ref.)	
Yes	99,616/1,901	1.99	0.57 (0.52-0.62)	<.0001
Family income level				
1st quartile	29,719/1,291	4.99	1 (Ref.)	
2nd quartile	20,182/514	3.27	0.70 (0.61-0.81)	<.0001
3rd quartile	38,708/811	2.36	0.53 (0.47-0.60)	<.0001
4th quartile	47,202/839	1.90	0.48 (0.42-0.54)	<.0001
Educational level				
None	5,945/348	5.98	1 (Ref.)	
Primary	14,099/443	3.82	0.77 (0.63-0.95)	0.0144
Secondary	64,524/1,625	2.93	0.63 (0.51-0.77)	<.0001
Tertiary	51,243/1,039	2.14	0.49 (0.39-0.61)	<.0001
Occupation				
Manager/professional	17,180/350	2.15	1 (Ref.)	
Clerical	15,608/287	1.89	0.85 (0.71-1.01)	0.0704
Service/sales	20,496/538	3.00	0.99 (0.84-1.16)	0.8705
Agricultural/forestry/fishery	13,269/206	1.47	0.53 (0.42-0.67)	<.0001
Technician/operator	29,562/530	1.98	0.80 (0.67-0.95)	0.0095

	No depression/depression	Weighted prevalence (%)	AOR (95% CI)†	*P-value*
Housewife	18,437/714	3.68	1.08 (0.91-1.27)	0.38
Unemployed	15,665/711	4.59	1.55 (1.30-1.84)	<.0001
Others	5,594/119	2.37	0.67 (0.51-0.87)	0.0023
Alcohol intake (g/day)				
<5.0	82,694/2,121	2.62	1 (Ref.)	
5.0–14.9	26,213/627	2.49	1.03 (0.91-1.16)	0.6921
15.0–29.9	17,131/379	2.50	1.06 (0.92-1.24)	0.4203
30+	9,773/328	3.90	1.62 (1.36-1.91)	<.0001
Drinking initiation age				
<19	35,272/1,188	3.58	1 (Ref.)	
19+	100,539/2,267	2.30	0.63 (0.57-0.69)	<.0001
Attempt to cut down/quit drinking				
No	116,896/2,551	2.28	1 (Ref.)	
Yes	18,915/904	4.98	2.11 (1.91-2.34)	<.0001
Hypertension				
No	105,091/2,587	2.62	1 (Ref.)	
Yes	30,720/868	2.87	1.14 (1.00-1.29)	0.0448
Diabetes mellitus				
No	124,289/3,035	2.59	1 (Ref.)	
Yes	11,522/420	3.69	1.44 (1.23-1.69)	<.0001

Relationship between alcohol flushing response and depression by alcohol intake. Among the participants who drink less than 5 grams of alcohol per day and within 5 to 14.9 grams of alcohol per

day, current flushers had significantly higher odds of depression than never flushers (<5 g/day: AOR=1.21, 95% CI=1.08-1.36, P-value=0.1×10^{-3}; 5.0-14.9 g/day: AOR=1.40, 95% CI=1.14-1.71, P-value=0.1×10^{-3}). No significant associations were seen among groups who drink above 15 g/day alcohol. (Table 3).

Table 3

Association between alcohol flushing response and depression in participants with different drinking amount (<5 g/day, 5-14.9 g/day, 15-29.9 g/dy, 30+ g/day) (n=139,266). †OR adjusted sex, age, obesity, smoking status, exercise, social activity, family income level, education level, occupation, alcohol intake, drinking initiation age, attempt to cut down/quit drinking, hypertension, and diabetes mellitus. Abbreviation: AOR, adjusted odds ratio; CI, confidence interval; Ref, reference; BMI, body mass index.

Alcohol intake (g/day)	Alcohol flushing response	AOR (95% CI)†	*P-value*
<5.0	Never flushing	1 (Ref.)	
	Former flushing	1.07 (0.81-1.40)	0.001
	Current flushing	1.21 (1.08-1.36)	<.0001
5.0-14.9	Never flushing	1 (Ref.)	
	Former flushing	1.00 (0.59-1.68)	0.0013
	Current flushing	1.40 (1.14-1.71)	<.0001
15.0-29.9	Never flushing	1 (Ref.)	
	Former flushing	1.01 (0.59-1.75)	0.0993
	Current flushing	1.27 (0.96-1.69)	<.0001
30+	Never flushing	1 (Ref.)	
	Former flushing	0.81 (0.46-1.42)	0.6327
	Current flushing	0.94 (0.72-1.22)	<.0001

Discussion

In a large community sample of Korean adult drinkers, we investigated the prevalence of the alcohol flushing response and its association with depression. We found that more than one-third of participants were current flushers, and there was a significant link between the current flushing response and depression. Unlike previous studies that identified the prevalence of alcohol flushers in a relatively small number of subjects, this large study sample was more representative of the actual population. Our findings help clarify the distribution of the alcohol flushing response among drinkers in the Korean population and help strengthen the evidence for an underlying relationship between the flushing response and depression.

The prevalence of the alcohol flushing response concurs with previous findings within the range of 36–45%[1,2]. The relationship of the flushing response and depression is consistent with recent findings that the alcohol flushing genotype (ALDH2*2 heterozygote) confers a higher risk of depression compared with those less sensitive to alcohol[11]. Our study supports this finding in a larger population sample. While Yoshimasu et al. (2016) evaluated 25 subjects with depression among 602 study participants and 12 subjects with depression among those with a flushing response genotype (ALDH2*1/*2 and ALDH2*2/*2), we evaluated 1,304 subjects with depression among 48,925 current flushers.

Several studies claim that people with inactive ALDH2 are protected from alcohol-associated risks because they have a greater tendency to abstain from drinking[7] and thus have a reduced chance of developing AUDs and depression related to AUDs[8]. Our study corresponds with this idea as the current flushers generally drink less frequently and smaller amounts compared with never flushers. Nevertheless, the presence of current flushing response increases the risk of depression, regardless of the amount of alcohol consumed. Despite similarly small amounts of alcohol consumed among never and current flushers, the current flusher was found to have a higher risk of depression. This indicates that current flushers may have a lower threshold to alcohol-induced depression, compared to the never flushers. The current flushers may experience the mechanisms of acetaldehyde contributing to causing depressive states, as they react more sensitively to a small dose of alcohol[5].

Recently, Zhu et al. (2020)[12] suggested contrary results from Mendelian randomization (MR) in 476 middle-aged and older Chinese adults (average age 49.4 years); a protective effect of alcohol was found for depression using flushing response as an instrumental variable (IV). MR studies are usually perceived as superior to observational studies, as genetic variants used as IVs are inherited and not affected by confounders. Yet, estimates from MR studies can sometimes be interpreted as biased evidence of causality, as they may differ by subgroup[13]. The studies mentioned in Zhu et al. (2020)[12] had different results regarding alcohol use and depression according to country, average age of the study population, and definition of alcohol use/consumption, even in studies using a MR framework. For example, a study of elderly males conducted in Australia showed that alcohol consumption had no significant effect on depression, even when using an ADH1B genetic polymorphism as an IV[14]. Genetic variants that do not adequately explain the variation in exposure may also provide biased causal estimates[13]. A large sample size (> 500) is considered a partial solution to the problem. Although we could not use IV estimators, our results were derived from a large (139,266) general population. Further studies should generalize the relationship between alcohol consumption and depression, perhaps using an MR framework for the general population.

Our results should be carefully interpreted for the following limitations. First, we did not consider non-drinkers in our analysis. The comparison between non-drinkers and drinkers could help develop deeper insight into how alcohol flushing response affects alcohol drinking behavior, and how crucial alcohol drinking could be in causing depression among people with alcohol flushing genotype. Second, this study does not cover the biochemical mechanisms underlying the relationship between the alcohol flushing

response and depression. Third, a characteristic of alcohol flushers in this study was varied from the characteristic of inactive ALDH2, although the alcohol flushing response is a well-known proxy for inactive ALDH2. Contrary to the characteristic of inactive ALDH2, in which ALDH2*2/*2 homozygotes are unable to drink significant amounts of alcohol, many flushing individuals in our study were found to drink more than 30 g alcohol per day. Last, since the analysis used a secondary source for a cross-sectional study, there are some restrictions in the interpretation. A variable such as alcohol intake is measured during an intermediate course of one's life, and there could be unmeasured confounders. Thus, further studies are necessary to reinforce our findings.

Declarations

Author Contributions

S.J. conducted the statistical analyses and wrote the manuscript. S.J., H.K., I.C., S.C. contributed to the study design and approved the final manuscript.

Additional Information

The authors declare no competing interests.

References

1 Brooks, P. J., Enoch, M. A., Goldman, D., Li, T. K. & Yokoyama, A. The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. *PLoS Med***6**, e50, doi:10.1371/journal.pmed.1000050 (2009).

2 Enoch, M. A. Genetic influences on response to alcohol and response to pharmacotherapies for alcoholism. *Pharmacol Biochem Behav***123**, 17-24, doi:10.1016/j.pbb.2013.11.001 (2014).

3 Crabb, D. W., Edenberg, H. J., Bosron, W. F. & Li, T. K. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. *J Clin Invest***83**, 314-316, doi:10.1172/JCI113875 (1989).

4 Hishida, Y. M. I. I. Y. T. T. K. S. F. J. A. S. Relationship between facial flushing and blood acetaldehyde levels after alcohol intake. *Pharmacology Biochemistry and Behavior***10**, 303-311, doi:https://doi.org/10.1016/0091-3057(79)90105-9 (1979).

5 Brancato, A., Lavanco, G., Cavallaro, A., Plescia, F. & Cannizzaro, C. Acetaldehyde, Motivation and Stress: Behavioral Evidence of an Addictive menage a trois. *Front Behav Neurosci***11**, 23,

doi:10.3389/fnbeh.2017.00023 (2017).

6 Boden, J. M. & Fergusson, D. M. Alcohol and depression. *Addiction***106**, 906-914, doi:10.1111/j.1360-0443.2010.03351.x (2011).

7 Crabb, D. W., Matsumoto, M., Chang, D. & You, M. Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genesis of alcohol-related pathology. *Proc Nutr Soc***63**, 49-63, doi:10.1079/pns2003327 (2004).

8 Yoshimasu, K. *et al.* Genetic alcohol sensitivity regulated by ALDH2 and ADH1B polymorphisms is strongly associated with depression and anxiety in Japanese employees. *Drug Alcohol Depend***147**, 130-136, doi:10.1016/j.drugalcdep.2014.11.034 (2015).

9 Manninen, L., Poikolainen, K., Vartiainen, E. & Laatikainen, T. Heavy drinking occasions and depression. *Alcohol Alcohol***41**, 293-299, doi:10.1093/alcalc/agh246 (2006).

10 Pietraszek, M. H. *et al.* Alcohol-induced depression: involvement of serotonin. *Alcohol Alcohol***26**, 155-159, doi:10.1093/oxfordjournals.alcalc.a045096 (1991).

11 Yoshimasu, K. Depression, Alcoholism, and Genetic Alcohol Sensitivity Regulated by ALDH2 and ADH1B Polymorphisms among Japanese Community-Dwelling Adults. *Archives of Depression and Anxiety*, 037-043, doi:10.17352/2455-5460.000013 (2016).

12 Zhu, C. *et al.* Alcohol Use and Depression: A Mendelian Randomization Study From China. *Front Genet***11**, 585351, doi:10.3389/fgene.2020.585351 (2020).

13 Savla, J. & Neeland, I. J. The Pros and Cons of Mendelian Randomization Studies to Evaluate Emerging Cardiovascular Risk Factors. *Current Cardiovascular Risk Reports***12**, 2, doi:10.1007/s12170-018-0566-9 (2018).

14 Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J. & Flicker, L. The triangular association of ADH1B genetic polymorphism, alcohol consumption and the risk of depression in older men. *Mol Psychiatry***19**, 995-1000, doi:10.1038/mp.2013.117 (2014).

15 Kroenke, K., Spitzer, R. L. & Williams, J. B. W. The PHQ-9. *Journal of General Internal Medicine***16**, 606-613, doi:https://doi.org/10.1046/j.1525-1497.2001.016009606.x (2001).

16 Shin, C. M., Kim, N., Cho, S. I., Sung, J. & Lee, H. J. Validation of Alcohol Flushing Questionnaires in Determining Inactive Aldehyde Dehydrogenase-2 and Its Clinical Implication in Alcohol-Related Diseases. *Alcohol Clin Exp Res***42**, 387-396, doi:10.1111/acer.13569 (2018).

17 Greenfield, T. K. & Kerr, W. C. Alcohol measurement methodology in epidemiology: Recent advances and opportunities. *Addiction***103**, 1082-1099, doi:10.1111/j.1360-0443.2008.02197.x (2008).

18 Welfare, M. o. H. a. Action plan to prevent the harmful use of alcohol. *Ministry of Health and Welfare* (2018).

19 Pan, W.-H. Y., Wen-Ting How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pacific journal of clinical nutrition***17**, 370-374 (2008).