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Alcohol Flushing Response and the Risk of Depression

알코올 홍조 반응과 우울증의 관계

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이 논문을 보건학석사 학위논문으로 제출함

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Abstract

Background: Alcohol flushing response is a physiological response caused by an excessive accumulation of toxic acetaldehyde from alcohol intake, which occurs around 36–45% of East Asians. Although it is known to be a risk factor for health outcomes associated with alcohol intake, its relationship with depression is relatively less known. Besides, the prevalence of alcohol flushing cases of general populations in Korea is not yet established. Thus, this study aims to identify the prevalence of alcohol flushing in Korean population, and to evaluate the association between alcohol flushing and the risk of depression in general population.

Methods: Using the data from 2019 Korean Community Health Survey (KCHS), 139,285 participants were included in the analysis. Only the current drinkers were included in the analysis. Patient Health Questionnaire 9 (PHQ-9) was used to identify participants with depression. Two specific questionnaires for assessing current and former flushing status were used to identify the presence of alcohol flushing response. Calculation of non-weighted frequency and weighted percentages was done to provide descriptive characteristics of study participants, and logistic regression analysis was done to find the relationship between alcohol flushing response and depression. To test whether alcohol intake and occupation moderate the association between alcohol flushing response and depression, the relative excess risk due to interaction

(RERI) were calculated. All the analyses were done using SAS 9.4.

Results: Around 60% of study participants were never flushers, 35% were current flushers, and 4% were former flushers. The prevalence of depression was 2.52% for never flushers, 2.93% among current flushers and 2.63% among former flushers. Although no association were found between former flushing response and depression, the relationship was significant among current flusher and depression. Compared to the never flushers, current flushers had 1.22 times the odds of depression (AOR=1.22, 95% CI=1.12−1.34). Compared to the participants who drink less than 5 g/day alcohol, depression risk significantly increased among never flushers who drink above 15 g/day (15−29.9 g/day: AOR=1.28, 95% CI=1.07−1.53), and the depression risk significantly increased among current flushers who drink 5−15 g/day and 30 g/day (5−14.9 g/day: AOR=1.25, 95% CI=1.03−1.52; above 30g/day: AOR=1.64, 95% CI=1.01−2.21). The quantity of alcohol intake did not moderate the risk of depression in current flushers.

Conclusions: This study contributes to clarifying the prevalence of alcohol flushing population among the Korean adult drinkers, and the association between the alcohol flushing response and depression. A significant number of Korean drinkers were found to be alcohol flushers, and they were more likely to develop depression. Therefore, alcohol flushing response could serve as a useful and significant indicator for predicting depression. Furthermore, the association between the flushing response and depression may be

due to the low threshold alcohol flushers has to alcohol induced depression, or due to a certain circumstances (i.e. non-manager/professional occupations) that makes flushers drink beyond their limit or will. These evidences, therefore, would contribute in preventing and decreasing the prevalence of depression among the general population.

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Keywords : Alcohol flushing response, inactive ALDH2, depression, PHQ-9

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Abbreviations

ALDH2 : aldehyde dehydrogenase 2

ADH1B : alcohol dehydrogenase 1B

AOR : adjusted odds ratio

AUD : alcohol-use disorder

BMI : body mass index (kg/m2)

g/day : grams of alcohol per day

GF : graduated frequency

KCDA : Korea Disease Control and Prevention Agency

KCHS : Korean Community Health Survey

KRW : Korean Republic Won

Ref : reference

RERI : relative excess risk due to interaction

SD : standard deviation

보존용 학위논문 정오표

페이지	정정 전	정정 후
p. 1 (표지)	2021년 2월	2021년 8월
p. 15; 6	(트레드모니터, 2020)	(트렌드모니터, 2020)
p. 40; 30	Table 10. Association between daily alcohol intake and depression in never flushing and current flushing participants (n=139,285).	Table 10. Association between daily alcohol intake and depression in never flushing and current flushing participants (n=139,285)
p. 29; 20	Around 70%of participants	Around 70% of participants
p. 45; 36	general population of 132,955 current drinkers	general population of 139,285 current drinkers

Chapter 1. Introduction

1.1. Study Background

1.1.1. Depression

Depression is one of the major causes of disease burden related to mental health. Depression may cause depressive thoughts, negatively influence the quality of life, disable normal functioning (Liu et al., 2020), or even leads to suicide (WHO, 2020). Globally, it is assumed that more than 264 million people are suffering from depression (James et al., 2017). In 2019, depressive disorders were among the top ten causes of disability-adjusted life years (DALYs) in the age group within 25 to 49 years (Vos et al., 2020). South Korea was rated as the second-highest country with an increase in the age-standardized incidence of depression in 2017 (Liu et al., 2020).

As a complex interaction of social, psychological and biological factors contributes to depression (Vos et al., 2020), a thorough understanding is necessary for an effective intervention to lower the prevalence of depression among the general population. The identification of a specific group that is at risk for depression would facilitate the interventions for preventing and recovering the symptom.

1.1.2. Alcohol flushing response

Alcohol flushing is a physiological response to alcohol intake that 36% to 45% of East Asians (Koreans, Chinese, and Japanese) experience (Brooks et al., 2009; Enoch et al., 2014). It is a distinguishing characteristic found among the carriers of a mutant ALDH2*2 alleles, so-called inactive ALDH2. Since ALDH2 is in charge of encoding the major enzyme that eliminates toxic acetaldehyde derived from alcohol, the individuals with inactive ALDH2 are unable to or slower at metabolizing acetaldehyde (Crabb et al., 1989). The homozygotes of this genotype (ALDH2*2/*2) does not have detectable ALDH2 activity and the heterozygotes (ALDH2*1/*2) have reduced function of ALDH2 activity, of more than 100-fold (Brooks et al., 2009). Consequently, alcohol-derived acetaldehyde excessively accumulates in these individuals and leads to symptoms such as facial flushing, nausea, and tachycardia even after small amounts of alcohol consumed (alcohol flushing response) (Brooks et al., 2009).

Figure 1. The Alcohol Flushing Response

Facial flushing in a 52-year-old before (left) and after (right) drinking a glass of beer. Written consent for the publication of the individual photographed in this figure was obtained.

Studies have shown that the presence of the specific genotype is associated with the risk of esophageal cancer, cardiovascular health, and some other health outcomes associated with alcohol drinking, due to excessive accumulation of acetaldehyde after drinking (Andrici&Sharon&Hu, 2016; Shin et al., 2017; Boiccia, 2009). On the other hand, some studies insists that the carriers of inactive ALDH2 are protected against the risks associated with alcohol (Shin et al., 2018), such as alcoholism (Yoshimasu, 2015 a) or cardio-metabolic diseases (Taylor, 2015; Ota, 2016), and ALDH2*2/*2 homozygotes are protective to esophageal cancer (Brooks et al., 2009). Particularly due to the intense symptoms that the carriers of inactive ALDH2 experience after alcohol consumption (alcohol flushing response).

1.1.3. Alcohol flushing response and the risk of depression

The excessive accumulations of acetaldehyde could be a considerable cause of depression. The alcohol flushers are particularly unprotected since they are incapable of metabolizing acetaldehyde effectively and experience a significant rise in blood acetaldehyde concentrations after drinking alcohol while non-flushers do not (Mizoi et al., 1979). Acetaldehyde may contribute to causing anxious or depressive states by bidirectional effects on corticotropin-releasing hormone and Neuropeptide Y, which are the two major stress-related peptides that are functionally opposite (Brancato et al., 2017). In addition, due to the contribution of acetaldehyde in the development of the traits of alcohol-use

disorders (AUD), alcohol flushers may be more vulnerable to AUD induced depression, even if they drink less than non-flushers. The interaction between acetaldehyde and dopamine is known to lead to the development of addictive behavior that is highly relevant to AUD, which may accompany mental disorders such as depression (Brancato et al., 2017). It is problematic since the presence of alcohol use disorder is known to double the risks of major depression (Boden & Fergusson, 2011).

As known so far, the number of flushers with excessive drinking behavior may not be large. Nonetheless, alcohol flushers may experience the adverse mechanisms of alcohol, involving depression, even with a smaller amount of alcohol intake compared to the non-flushers. Normally, heavy drinking is considered to increase the risk of depression (Manninen, 2006). Often after heavy drinking occasions, it is observed that people experience alcohol withdrawal symptoms; these symptoms are associated with the decrease of the concentration of blood serotonin levels, which explains the neural mechanism of depression (Pietraszek, 1991).

1.1.4. Public health impact of the study

Simply having an alcohol flushing response is not an obstacle, but if those individuals are exposed to a certain drinking culture, forced or over-drinking, the presence of the flushing reaction can be an obstacle that increases the risk of depression. In these circumstances, having the flushing response is not an individual problem but a social problem that requires national attention and

intervention. This would be the solution to form the right drinking culture in Korean society.

Often in Korea, people face instances where they have to drink against their will. A statistic shows that at drinking occasions with work colleagues after work, so-called 'Hoe-Shik' in Korean, 9.2% said they were forced to drink, and 19.2% said they didn't want to but were reluctant to attend Hoe-Shik because of the atmosphere (오재환, 2002). In some circumstances, when people say they cannot drink or should not drink much because they have an alcohol flushing response, people tend to ignore this opinion and rather encourage them to drink more to diminish the response. These circumstances could facilitate the accumulation of acetaldehyde in people with alcohol flushing genotype. Still in Korea, the act of refusing someone's drinking offer is considered to be against drinking etiquette, especially when a superior person suggests drinking (Son & Lee, 2009). A study have shown that for the reasons why college students or workers drank against their will, 39.8% answered 'due to persistent recommendations from bosses, seniors, professors, etc.' and 30.4% answered 'to avoid disadvantages of not participating in drinking occasions' (인크루트, 2016). Thus, in these situations where people have to drink against their will, flushing individuals, with a genetic trait that cannot metabolize alcohol well, have a high chance to exceed their drinking threshold. Besides, people who are repeatedly exposed to these drinking circumstances may be more stressed by these

drinking cultures, which consequently could result in depression. A survey revealed that 51.4% of workers are having stress due to issues regarding Hoe-Shik (트레드모니터, 2020).

1.2. Purpose of Research

This study will answer the following study questions through the investigation of the prevalence of alcohol flushing response in the Korean population, and clarification of the association between alcohol flushing response and depression.

1. Why is it necessary to study the depression risk of alcohol flushing population?

2. Is there a link between alcohol flushing response and depression?

3. What are the reasons for the link between the flushing response and depression?

- Is it due to the low drinking threshold alcohol flushers have?
- Is it due to the synergic effect of alcohol flushing response and the amount of alcohol intake?

Chapter 2. Methods

2.1. Data sources and Study participants

This study was performed by using the data from a survey conducted by Korea Disease Control and Prevention Agency (KCDA): 2019 Korean Community Health Survey (KCHS). It is a community-based cross-sectional survey that aims to provide data that could be utilized in planning, implementing, monitoring, and evaluating health promotion of the community and programs for disease prevention. The major subjects covered in this survey are the personal health practices and behaviors that are associated with diseases, such as smoking, alcohol use, drinking and driving, and physical activities.

In the analysis, a total of 139,285 populations were included. Among the total of 229,099 participants completed 2019 KCHS, 82,767 were subsequently excluded for non-drinkers and 7,047 missing values of grade at depression, alcohol flushing, sex, age, obesity status, smoking status, physical activity, family income level, educational level, alcohol intake, drinking initiation age, and attempt to cut down/quit drinking to avoid any selection bias. The final study population was set as current drinkers only.

The Institutional Review Board (IRB) at Seoul National University approved with study (IRB Number: E2106/002-002).

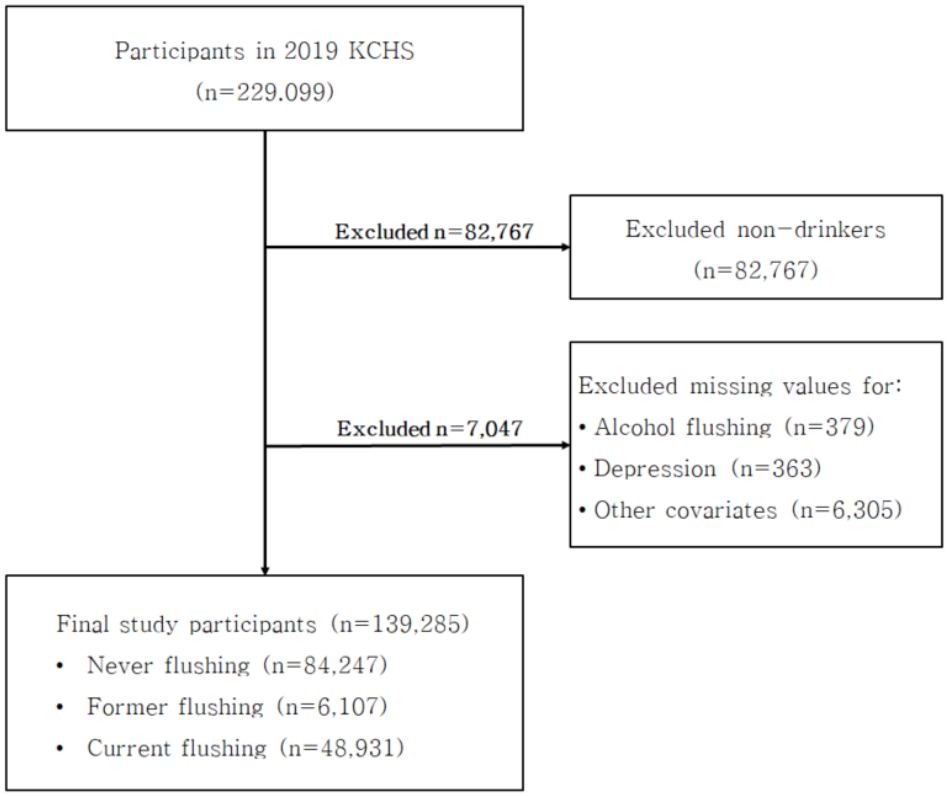

Figure 2. Flow chart of study participants

2.2. Measurements

2.2.1. Depression

The presence of depression was identified by Patient Health Questionnaire 9 (PHQ-9), which is a simple measure that aligns with the measure for major depression, DSM-IV criteria (Kroenke et al., 2001). The frequency of depression related symptoms are rated based on the respondents' experience over the past two weeks (four-point scale, from not at all to nearly every day), and the scores are summed to provide an index of depressive symptoms. Respondents who scored more than 10, within 0 to 27 of the PHQ-9 score range, were identified as people with depression in this study.

2.2.2. Alcohol flushing response

The presence of current alcohol flushing response was identified by questionnaire assessing current and former flushing status: (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 'yes' to question (a) were classified as 'current flushing', who answered 'no' to question (a) but 'yes' to question (b) were classified as 'former flushing', and who answered 'no' to both questions were classified as 'never flushing'. These questionnaires were proven to be a valid tool for detecting inactive ALDH2 with 95.1% sensitivity

and 76.5% specificity among Korean population (Shin et al., 2018).

2.2.3. Alcohol intake

Alcohol intake as grams of alcohol consumed per day (g/day) was obtained by graduated frequency (GF) measure (Greenfield & Kerr, 2008). I 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) (보건복지부, 2018). The values used for quantities were the arithmetic mid−points of the number of drinks consumed per occasion (approximate mid−points) were: 0, 6, 12, 36, 120, and 264. Thus, the alcohol intake was classified in to four categories: <5 g/day, 5−14.9 g/day, 15−29.9 g/day, and above 30 g/day.

2.2.4. Occupation

Participants' occupation status was used as a cultural aspect of alcohol drinking among Koreans. The occupation status was categorized into eight categories: managers or professional, clerical workers, service and sales workers, agricultural, forestry and fishery workers, technicians and operators, house−wife, unemployed, and others.

2.2.5. Covariates

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.

The age was categorized as 19 to 39 years, 40 to 59 years, 60 to 69 years, and 70 years or above. Obesity status was categorized as yes or no (BMI $\geq$25.0, BMI <25.0). Smoking status was categorized 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). Educational level was categorized as none, primary education, secondary education, tertiary education. Income level was categorized into four quantiles. Social activity was categorized as yes or no.

2.3. Statistical analysis

Unweighted frequency and weighted percentages were calculated to provide for the descriptive characteristics of the study participants. Considering that KCHS data is a complex sample design, individual weights were applied to estimate the population. The age, family income level, and alcohol intake was exceptionally presented with mean and its standard deviation.

Chi-squared statistics were derived to assess the statistical significance of differences of depression. Multiple logistic regression models were used to estimate associations between alcohol flushing and depression, adjusting for sex, and age. The association between daily alcohol intake and depression was measured in never flushing and current flushing participants separately by stratification analysis, adjusting for sex, age, obesity, smoking status, exercise, social activity, family income level, educational level, and occupation.

To examine the additive interaction of alcohol flushing response and alcohol intake, the participants with former flushing response (n=6,107) were excluded in the analysis. Four subgroups were created for each alcohol consumption amount divided by different cut-lines and alcohol flushing response. The three different cut-lines for alcohol consumption amount were: 5 g/day, 15 g/day, 30 g/day. For example, the subgroups for alcohol intake with 5 g/day cut-line and the flushing response were: (1) participants who drink

less than 5 g/day and never flusher (reference group), (2) participants who drink less than 5 g/day and current flusher, (3) participants who drink more than 5 g/day and never flusher, and (4) participants who drink more than 5 g/day and current flusher. The additive interactions were estimated by the relative excess risk due to interaction (RERI). RERI can be expressed as the following equation: $OR_{AB} - OR_A - OR_B + 1$. When the RERI > 0 and the lower limit of 95% CI > 0, it indicates positive interaction, and the vise versa. (VanderWeele & Knol, 2014). The 95% CI of this measure were calculated by the delta methodology (Hosmer & Lemeshow, 1992).

Analysis was conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA). The level of statistical significance was set as <0.05, and all p values were two-sided.

Chapter 3. Results

3.1. Descriptive characteristic of study participants

A total of 139,285 current drinkers were included in this study. Overall, there was slightly more male participants (n=73,798) than female (n=65,487), and the average age was around 45 years old. More than half of the participants were never smokers, and around one-thirds of participants exercise. While the distribution of the participants' obesity status, smoking status, and exercise was similar to the overall prevalence, regardless of depressive status, the distribution of sex, age and social activity were different. There were more female than male in participants with depression, while there were more male in those without depression. Besides, more than half of the participants with depression where aged within 19-39 years old, whereas high proportion of participants without depression were within 40-59 years old. While the proportion of people who does social activity exceeds two-third in people without depression, it only reached about half in people with depression. The distribution of obesity status did not vary significantly within the presence of depression (Table 1).

Table 1. General characteristic of study participants by depressive status

	N(%)			
	Total (n=139,285)	Depression (n=3,457)	No depression (n=135,828)	P-value
Sex				
Male	73,798	1,286 (39.3)	72,512 (56.4)	<0.001
Female	65,487	2,171 (60.7)	63,316 (43.6)	
Age (years)				
19-39	39,506	1,270 (50.2)	38,236 (39.0)	<0.001
40-59	57,445	1,102 (31.3)	56,343 (42.9)	
60-69	24,365	499 (9.6)	23,866 (11.3)	
70+	17,969	586 (8.9)	17,383 (6.8)	
Mean±SD	44.9±0.06	42.6±0.24	45.0±0.06	
Obesity status				
No (BMI <25.0)	88,735	2,267 (65.7)	86,468 (64.6)	0.308
Yes (BMI ≥25.0)	50,550	1,190 (34.3)	49,360 (35.4)	
Smoking status				
Never smoker	80,596	2,039 (58.7)	78,557 (57.7)	<0.001
Ex-smoker	29,271	512 (13.5)	28,759 (20.0)	
Current smoker	29,418	906 (27.8)	28,512 (22.3)	
Exercise				
No	103,283	2,708 (77.8)	100,575 (74.2)	<0.001
Yes	36,002	749 (22.2)	35,253 (25.8)	
Social activity				
No	37,754	1,555 (46.7)	36,199 (28.2)	<0.001
Yes	101,531	1,902 (53.3)	99,629 (71.8)	
Family income level				
1st quantile	31,020	1,293 (27.1)	29,727 (14.1)	<0.001
2nd quantile	20,697	514 (15.8)	20,183 (12.8)	
3rd quantile	39,524	811 (26.5)	38,713 (30.0)	
4th quantile	48,044	839 (30.6)	47,205 (43.2)	
Mean±SD (10,000 KRW)	457.3±1.59	381.3±4.94	459.3±1.59	
Educational level				
None	6,295	348 (4.0)	5,947 (1.7)	<0.001
Primary	14,544	444 (7.7)	14,100 (5.3)	
Secondary	66,156	1,626 (50.6)	64,530 (45.8)	
Tertiary	52,290	1,039 (37.7)	51,251 (47.2)	
Occupation				
Manager/professional	17,531	350 (13.1)	17,181 (16.3)	<0.001
Clerical	15,896	287 (10.3)	15,609 (14.6)	
Service/sales	21,037	538 (17.4)	20,499 (15.4)	
Agricultural/forestry/ fishery	13,477	206 (1.5)	13,271 (2.7)	
Technician/operator	30,095	530 (16.0)	29,565 (21.6)	
House-wife	19,154	715 (18.2)	18,439 (13.0)	
Unemployed	16,378	712 (18.2)	15,666 (10.3)	
Others	5,717	119 (5.4)	5,598 (6.1)	

Descriptive data are provided as unweighted frequencies (N) with weighted percentages (%).

Abbreviation: SD, standard deviation; BMI, body mass index (kg/m2); KRW, Korean Republic Won.

The participants' average family income level was significantly higher among participants without depression. The distribution of educational level was highly concentrated in the secondary level among participants with depression, and the concentration was the highest in tertiary level among participants without depression. Among the eight different occupation, the proportion of house-wife and unemployed were high among depressive individuals (both 18.2%), and the proportion was the highest among technician or operator (21.6%) followed by manager/professional (16.3%) in people without depression.

Table 2 shows the characteristic of study participants according to their alcohol drinking behaviors and depressive status. Generally, participants with depression had significantly lower frequency of drinking, 40.3% drank monthly or less among participants with depression. On the other hand, the proportion of participants who drinks more than 10 drinks per occasion were 21%, which is significantly higher than the proportion of non-depressive participants who drink more than 10 drinks. When the drinking frequency and drinks per occasion is converted into daily alcohol intake, depressive participants consumed around 9 grams of alcohol per day, which is slightly more than a drink of alcohol, while non-depressive participants consumed around 8 grams of alcohol per day.

Table 2. Drinking characteristics of study participants by their alcohol drinking behaviors and depressive status (n=139,285)

N (%)

	Total (n=139,285)	Depression (n=3,457)	No depression (n=135,828)	P-value
Drinking frequency				
Monthly or less	52,282	1,449 (40.3)	50,833 (36.4)	<0.001
2-4 times per month	42,068	903 (27.6)	41,165 (32.8)	
2-3 times per week	29,602	619 (19.9)	28,983 (22.0)	
4 + times per week	15,333	486 (12.2)	14,847 (8.7)	
Drinks per occasion				
1-2	50,286	1,356 (33.9)	48,930 (32.5)	<0.001
3-4	29,790	639 (18.7)	29,151 (21.2)	
5-6	17,460	362 (11.8)	17,098 (13.3)	
7-9	23,222	465 (14.6)	22,757 (17.9)	
10+	18,527	635 (21.0)	17,892 (15.1)	
Daily alcohol intake (g/day)				
<5.0	84,825	2,123 (59.3)	82,702 (60.1)	<0.001
5.0-14.9	26,844	627 (19.2)	26,217 (20.6)	
15.0-29.9	17,513	379 (12.3)	17,134 (13.1)	
30+	10,103	328 (9.2)	9,775 (6.2)	
Mean±SD	8.2±0.04	9.4±0.21	8.19±0.04	

Descriptive data are provided as unweighted frequencies (N) with weighted percentages (%). 1 drink = 7g of alcohol.
Abbreviation: SD, standard deviation; g/day, grams per day.

3.2. Characteristics of participants according to alcohol flushing response

Table 3 shows the characteristic of study participants according to alcohol flushing response and depressive status. The proportion of never flushers were significantly higher among non-depressive participants (never flushing: 61.2%, current flushing: 57.7%), and the proportion of current flushers were slightly higher among depressive participants (current flushing: 38.3%, never flushing: 34.7%). The proportion of former flushers was similar across different depressive status.

Table 3. Alcohol flushing response characteristics of study participants by depressive status (n=139,285)

	N (%)		
Alcohol flushing response	Depression (n=3,457)	No depression (n=135,828)	P-value
Never flushing	1,992 (57.7)	82,255 (61.2)	
Former flushing	160 (4.0)	5,947 (4.1)	0.002
Current flushing	1,305 (38.3)	47,626 (34.7)	

Descriptive data are provided as unweighted frequencies (N) with weighted percentages (%).

Table 4 shows the general characteristic of study participants according to alcohol flushing response. The overall distributions of sex were similar across different flushing status (never, former, current), but the proportion of male was slightly higher in former flushers (58.6%). Overall, the proportion of 40–59 years old was above 40%, higher proportion of people were not obese, were never smoker, does not engage in physical activity, but engage in social activity.

The overall distributions of socioeconomic characteristics of study participants were similar across different flushing status. Around 70%of participants are concentrated in the third to fourth quantile level of the family income, and around 90% concentrated in the secondary to tertiary educational level. The most common occupation among never flushers were technician and operator, and the same in former flushers and current flushers (20.9%, 26.7%, 21.9%, respectively).

Table 4. General characteristics of study participants by alcohol flushing response (n=139,285)

	N (%)			
	Never flushing (n=84,247)	Former flushing (n=6,107)	Current flushing (n=48,931)	P-value
Sex				
Male	44,202 (55.7)	3,481 (58.6)	26,115 (55.9)	0.002
Female	40,045 (44.3)	2,626 (41.4)	22,816 (44.1)	
Age (years)				
19-39	25,339 (41.2)	1,135 (28.1)	13,032 (37.4)	<0.001
40-59	34,922 (42.3)	2,656 (47.9)	19,867 (42.6)	
60-69	13,766 (10.3)	1,350 (15.2)	9,249 (12.3)	
70+	10,220 (6.2)	966 (8.7)	6,783 (7.7)	
Obesity status				
No (BMI <25.0)	53,962 (64.8)	3,793 (63.1)	30,980 (64.6)	0.117
Yes (BMI ≥25.0)	30,285 (35.2)	2,314 (36.9)	17,951 (35.4)	
Smoking status				
Never smoker	49,433 (58.5)	3,167 (52.3)	27,996 (57.1)	<0.001
Ex-smoker	16,505 (18.7)	1,549 (23.3)	11,217 (21.4)	
Current smoker	18,309 (22.8)	1,391 (24.4)	9,718 (21.5)	
Exercise				
No	62,630 (74.3)	4,466 (74.0)	36,187 (74.3)	0.888
Yes	21,617 (25.7)	1,641 (26.0)	12,744 (25.7)	
Social activity				
No	23,341 (29.5)	1,616 (27.4)	12,797 (27.6)	<0.001
Yes	60,906 (70.5)	4,491 (72.6)	36,134 (72.4)	
Family income level				
1st quantile	17,891 (13.7)	1,622 (17.1)	11,507 (15.4)	<0.001
2nd quantile	12,256 (12.5)	967 (13.7)	7,474 (13.2)	
3rd quantile	23,969 (29.7)	1,633 (29.5)	13,922 (30.3)	
4th quantile	30,131 (44.0)	1,885 (39.7)	16,028 (41.2)	
Educational level				
None	3,782 (1.7)	346 (2.4)	2,167 (1.8)	<0.001
Primary	8,133 (4.9)	841 (7.8)	5,570 (5.8)	
Secondary	39,341 (45.0)	3,110 (51.3)	23,705 (47.0)	
Tertiary	32,991 (48.5)	1,810 (38.6)	17,489 (45.4)	
Occupation				
Manager/professional	11,079 (16.9)	599 (13.2)	5,853 (15.5)	<0.001
Clerical	9,996 (14.9)	548 (12.5)	5,352 (14.0)	
Service/sales	12,715 (15.3)	900 (15.4)	7,422 (15.8)	
Agricultural/for-estry/fishery	7,692 (2.5)	748 (3.6)	5,037 (2.8)	
Technician/operator	17,801 (20.9)	1,559 (26.7)	10,735 (21.9)	
House-wife	11,649 (13.0)	793 (13.6)	6,712 (13.4)	
Unemployed	9,537 (10.0)	827 (11.4)	6,014 (11.2)	
Others	3,778 (6.6)	133 (3.6)	1,806 (5.5)	

Descriptive data are provided as unweighted frequencies (N) with weighted percentages (%).

Abbreviation: SD, standard deviation; BMI, body mass index (kg/m2); KRW, Korean Republic Won.

Table 5 shows the drinking characteristics of participants according to alcohol flushing response status. Overall, the drinking frequency of the participants is concentrated at the low level in all three groups of flushing status, whereas the drinks per occasions significantly vary among these groups. The number of individuals who drink less alcohol at a time (1−2 drinks per occasion) was more prevalent among current flushers than never flushers or former flushers. On the other hand, the number of participants who drinks 2−4 times per month was more prevalent among never flusher or former flusher. Consequently, while more than 20% never flushing or former flushing participants drink more than 15 grams of alcohol per day, the proportion was only 4.1% in current flushing participants.

Table 5. Drinking characteristics of study participants by alcohol flushing response status (n=139,285)

	Never flushing (n=84,247)	Former flushing (n=6,107)	Current flushing (n=48,931)	P−value
Drinking frequency				
Monthly or less	27,428 (31.0)	1,781 (27.7)	23,073 (47.2)	<0.001
2−4 times per month	26,411 (34.1)	1,764 (32.6)	13,893 (30.3)	
2−3 times per week	20,133 (25.0)	1,498 (25.5)	7,971 (16.3)	
4 + times per week	10,275 (9.9)	1,064 (14.2)	3,994 (6.3)	
Drinks per occasion				
1−2	26,361 (27.2)	1,901 (26.9)	22,024 (42.5)	<0.001
3−4	17,394 (20.1)	1,373 (22.4)	11,023 (22.7)	
5−6	11,237 (14.0)	783 (13.9)	5,440 (12.0)	
7−9	15,875 (20.2)	1,157 (20.1)	6,190 (13.1)	
10+	13,380 (18.5)	893 (16.7)	4,254 (9.6)	
Alcohol intake (g/day)				
<5.0	46,841 (54.1)	3,160 (51.0)	34,824 (71.5)	<0.001
5.0−14.9	18,060 (23.1)	1,332 (23.4)	7,452 (15.8)	
15.0−29.9	12,339 (15.5)	946 (15.7)	4,228 (8.6)	
30+	7,007 (7.3)	669 (9.9)	2,427 (4.1)	

Descriptive data are provided as unweighted frequencies (N) with weighted percentages (%). 1 drink = 7g of alcohol. Abbreviation: g/day, grams per day.

3.3. Association between alcohol flushing response and depression

Table 6 shows the prevalence of depression according to general characteristics when the participants were sub-divided according to the flushing status. Overall, the prevalence of depression was relatively high among current flushing population compared to the other alcohol flushing response status (never or former). The prevalence was especially high among current flushers who are female (4.05%), 19-39 years old (3.77%), who are obese (3.02%), who are current smoker (3.73%), who does not do physical activity (3.14%) or socialactivity (5.06%), who are in first quantile level of family income (5.34%), and who are house wife (4.18%).

Table 7 shows the prevalence of depression according to different drinking characteristics when the participants were sub-divided according to the flushing status. Compared to the other flushing status (never or current), high proportion of flushing population had depression when the drinking frequency was monthly or less (6.03%), when they drink more than 10 drinks per day (3.86%), and when the daily alcohol intake is above 30 grams (3.92%).

Table 6. Prevalence of depression according to alcohol flushing response and basic characteristics (n=139,285)

	N (Depression/no depression), % (Depression)					
	Never flushing (n=84,247)		Former flushing (n=6,107)		Current flushing (n=48,931)	
Total	1992/82255	2.52	160/5947	2.63	1305/47626	2.93
Sex						
Male	751/43451	1.77	70/3411	1.90	465/25650	2.04
Female	1241/38804	3.45	90/2536	3.66	840/21976	4.05
Age (years)						
19−39	788/24551	3.24	31/1104	2.83	451/12581	3.77
40−59	593/34329	1.75	71/2585	2.48	438/19429	2.23
60−69	259/13507	2.06	30/1320	2.61	210/9039	2.56
70+	352/9868	3.64	28/938	2.87	206/6577	3.30
Obesity status						
No (BMI<25.0)	1308/52654	2.61	103/3690	2.63	856/30124	2.88
Yes (BMI≥25.0)	684/29601	2.34	57/2257	2.64	449/17502	3.02
Smoking status						
Never smoker	1177/48256	2.53	90/3077	2.94	772/27224	3.00
Ex−smoker	288/16217	1.76	24/1525	1.40	200/11017	1.94
Current smoker	527/17782	3.08	46/1345	3.13	333/9385	3.73
Exercise						
No	1535/61095	2.60	124/4342	2.63	1049/35138	3.14
Yes	457/21160	2.28	36/1605	2.64	256/12488	2.30
Social activity						
No	876/22465	3.90	80/1536	4.87	599/12198	5.06
Yes	1116/59790	1.94	80/4411	1.79	706/35428	2.12
Family income level						
1st quantile	721/17170	4.85	69/1553	4.47	503/11004	5.34
2nd quantile	313/11943	3.32	22/945	3.93	179/7295	3.11
3rd quantile	461/23508	2.18	31/1602	1.67	319/13603	2.76
4th quantile	497/29634	1.79	38/1847	2.10	304/15724	2.09
Educational level						
None	214/3568	6.43	18/328	5.08	116/2051	5.37
Primary	239/7894	3.60	25/816	4.04	180/5390	4.15
Secondary	904/38437	2.71	79/3031	2.60	643/23062	3.36
Tertiary	635/32356	2.09	38/1772	2.23	366/17123	2.23
Occupation						
Manager /professional	221/10858	2.18	14/585	2.90	115/5738	2.02
Clerical	161/9835	1.73	10/538	1.38	116/5236	2.25
Service/sales	313/12402	2.81	19/881	2.34	206/7216	3.40
Agricultural /forestry/fishery	116/7576	1.36	12/736	1.54	78/4959	1.62
Technician /operator	287/17514	1.80	36/1523	2.62	207/10528	2.20
House−wife	397/11252	3.37	35/758	3.99	283/6429	4.18
Unemployed	427/9110	4.77	31/796	2.99	254/5760	4.58
Others	70/3708	2.07	3/130	2.15	46/1760	2.99

Descriptive data are provided as unweighted frequency (N) of people with and without depression, and weighted percentages (%) of participants with depression.
p−value($\chi 2$) were all <0.001 except obesity (never flushing: 0.047, former flushing: 0.978, current flushing: 0.405), occupation (former flushing: 0.072) variables.
Abbreviation: BMI, body mass index.

Table 7. Prevalence of depression according to alcohol flushing response and drinking characteristics (n=139,285)

	N (Depression/no depression), % (Depression)					
	Never flushing (n=84,247)		Former flushing (n=6,107)		Current flushing (n=48,931)	
Total	1992/82255	2.52	160/5947	2.63	1305/47626	2.93
Drinking frequency						
Monthly or less	725/26703	5.38	52/1729	5.76	672/22401	6.03
2-4 times per month	547/25864	2.16	37/1727	2.04	319/13574	2.46
2-3 times per week	399/19734	2.24	31/1467	2.52	189/7782	2.85
4 + times per week	321/9954	3.63	40/1024	3.34	125/3869	3.89
Drinks per occasion						
1-2	697/25664	2.62	53/1848	3.12	606/21418	2.92
3-4	339/17055	2.06	40/1333	3.12	260/10763	2.75
5-6	195/11042	2.13	17/766	1.89	150/5290	2.87
7-9	301/15574	2.03	23/1134	2.10	141/6049	2.62
10+	460/12920	3.68	27/866	2.45	148/4106	3.86
Alcohol intake (g/day)						
< 5	1120/45721	2.47	81/3079	2.69	922/33902	2.83
5 -14.9	386/17674	2.26	33/1299	2.29	208/7244	3.11
15-29.9	264/12075	2.38	21/925	2.34	94/4134	2.90
30+	222/6785	3.92	25/644	3.57	81/2346	3.92
< 5	1120/45721	2.47	81/3079	2.69	922/33902	2.83

Descriptive data are provided as unweighted frequency (N) of people with and without depression, and weighted percentages (%) of participants with depression among total subjects. 1 drink = 7g of alcohol.
p-value(χ2) were all <0.001 except drinks per occasion (former flusher: 0.203), and alcohol intake (former flushing: 0.336, current flushing: 0.133) variable.
Abbreviations: g/day, grams per day.

The association of alcohol flushing response was investigated through logistic regression analysis. Both the crude odds ratio (OR) and adjusted odds ratios (AOR) are shown in Table 8. As depicted in the table, the current flushing response is significantly associated with depression, both with and without the adjustment of confounding variables. Compared to the never flushers, the odds of depression was 1.17 times higher among current flushing participants without any adjustments of the confounders (OR=1.17, 95% CI=1.07−1.28), it was 1.19 times higher when adjusted for sex and age (AOR=1.19, 95% CI=1.08−1.30), and it was 1.22 times higher when all the confounders (sex, age, obesity, smoking status, exercise, social activity, family income level, educational level, occupation, and alcohol intake) were adjusted. In contrast, the OR and AORs of former flushing response were not statistically significant.

Table 8. Association between alcohol flushing response and depression (n=139,285)

	OR (95% CI)†	AOR (95% CI)[a]	AOR (95% CI)[b]
Alcohol flushing response			
Never flushing	1 (Ref.)	1 (Ref.)	1 (Ref.)
Former flushing	1.05 (0.85−1.29)	1.13 (0.92−1.39)	1.06 (0.86−1.31)
Current flushing	1.17 (1.07−1.28)***	1.19 (1.08−1.30)***	1.22 (1.12−1.34)***
Sex			
Male	−	1 (Ref.)	1 (Ref.)
Female	−	2.01 (1.84−2.19)***	3.01 (2.62−3.45)***
Age (years)			
19−39	−	1 (Ref.)	1 (Ref.)
40−59	−	0.57 (0.51−0.62)***	0.56 (0.50−0.62)***
60−69	−	0.67 (0.59−0.75)***	0.44 (0.38−0.52)***
70+	−	1.06 (0.93−1.21)	0.45 (0.37−0.54)***
Obesity			
No (BMI<25.0)	−	−	1 (Ref.)
Yes (BMI≥25.0)	−	−	1.11 (1.01−1.22)*
Smoking status			
Never smoker	−	−	1 (Ref.)
Ex−smoker	−	−	1.34 (1.14−1.57)***
Smoker	−	−	2.00 (1.75−2.30)***
Exercise			
No	−	−	1 (Ref.)
Yes	−	−	1.00 (0.91−1.11)
Social activity			
No	−	−	1 (Ref.)
Yes	−	−	0.57 (0.52−0.62)***
Family income level			
1st quantile	−	−	1 (Ref.)
2nd quantile	−	−	0.69 (0.60−0.79)***
3rd quantile	−	−	0.52 (0.45−0.59)***
4th quantile	−	−	0.46 (0.40−0.52)***
Educational level			
None	−	−	1 (Ref.)
Primary	−	−	0.79 (0.64−0.97)*
Secondary	−	−	0.62 (0.51−0.76)***
Tertiary	−	−	0.46 (0.37−0.58)***
Occupation			
Manager/professional	−	−	1 (Ref.)
Clerical	−	−	0.82 (0.68−0.98)*
Service/sales	−	−	0.98 (0.83−1.16)
Agricultural/forestry/fishery	−	−	0.52 (0.42−0.66)***
Technician/operator	−	−	0.79 (0.67−0.94)**
House−wife	−	−	1.08 (0.92−1.28)
Unemployed	−	−	1.59 (1.34−1.89)***
Others	−	−	0.62 (0.48−0.80)***
Alcohol intake (g/day)			
<5.0	−	−	1 (Ref.)
5.0−14.9	−	−	1.14 (1.01−1.29)*
15.0−29.9	−	−	1.24 (1.07−1.44)**
30+	−	−	1.99 (1.69−2.35)***

† OR of depression without any adjustments of the confounders.
[a] OR adjusted for sex, and age.
[b] OR adjusted for sex, age, obesity, smoking status, exercise, social activity, family income level, educational level, occupation, and alcohol intake.
Abbreviation: AOR, adjusted odds ratio; CI, confidence interval; Ref, reference. Level of statistical significance *<0.05, **<0.01, ***<0.001 .

3.4. Possible factor contributing to the association between alcohol flushing response and depression

To find out the factors contributing to the association between alcohol flushing response and depression, two major hypotheses were set. First, the link is due to the low threshold alcohol flushers has to alcohol. Second, the amounts of alcohol act as a moderator to the association. In order to verify the later hypotheses, only the never flushing and current flushing participants were included, and 6,107 former flushing participants were excluded from the analysis.

For 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), logistic regression analysis was performed using alcohol flushing response as an independent variable and development of depression as a dependent variable, after adjusting for confounding variables (sex, age, obesity, smoking status, exercise, social activity, family income level, educational level, and occupation) (Table 9). For each alcohol flushing response (never flushing, former flushing, and current flushing), logistic regression analysis was performed using daily alcohol intake as an independent variable and development of depression as a dependent variable, after adjusting for the confounding variables (Table 10).

Among 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 (below 5g/day: AOR=1.18, 95% CI=1.06–1.33; 5–14.9 g/day:

AOR=1.42, 95% CI=1.16-1.74).

Table 9. 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=139,285)

Alcohol intake (g/day)	Alcohol flushing response	AOR (95% CI)†
<5.0	Never flushing	1 (Ref.)
	Former flushing	1.10 (0.84-1.45)
	Current flushing	1.18 (1.06-1.33)**
5.0-14.9	Never flushing	1 (Ref.)
	Former flushing	1.08 (0.64-1.82)
	Current flushing	1.42 (1.16-1.74)***
15.0-29.9	Never flushing	1 (Ref.)
	Former flushing	1.02 (0.59-1.76)
	Current flushing	1.25 (0.94-1.66)
30+	Never flushing	1 (Ref.)
	Former flushing	0.88 (0.50-1.54)
	Current flushing	0.96 (0.74-1.24)

† OR adjusted for sex, age, obesity, smoking status, exercise, social activity, family income level, educational level, and occupation.
Abbreviation: AOR, adjusted odds ratio; CI, confidence interval; Ref, reference; BMI, body mass index.
Level of statistical significance *<0.05, **<0.01, ***<0.001 .

In the never flushing group, depression risk significantly increased among those drinking above 15 grams of alcohol per day (15-29.9 g/day: AOR=1.28, 95% CI=1.07-1.53; above 30 g/day: AOR=2.21, 95% CI=1.79-2.73) in respect to those who drink less than 5 grams of alcohol per day.

In the current flushing group, depression risk significantly increased among those drinking 5 to 14.9 grams of alcohol per day and above 30 grams of alcohol per day (5-14.9 g/day: AOR=1.25, 95% CI=1.03-1.52; above 30g/day: AOR=1.64, 95% CI=1.01-2.21) in respect to those who drink less than 5 grams of alcohol per day.

Table 10. Association between daily alcohol intake and depression in never flushing and current flushing participants (n=139,285).

Alcohol intake (g/day)	AOR (95% CI)†		
	Never flushing (n=84,235)	Former flushing (n=6,107)	Current flushing (n=48,917)
<5.0	1 (Ref.)	1 (Ref.)	1 (Ref.)
5.0–14.9	1.09 (0.93–1.27)	1.21 (0.80–1.83)	1.25 (1.03–1.52)*
15.0–29.9	1.28 (1.07–1.53)**	1.25 (0.74–2.13)	1.19 (0.91–1.56)
30+	2.21 (1.79–2.73)***	1.82 (1.12–2.96)*	1.63 (1.20–2.21)**
Sex			
Male	1 (Ref.)	1 (Ref.)	1 (Ref.)
Female	3.19 (2.67–3.80)***	2.40 (1.46–3.95)***	2.81 (2.23–3.55)***
Age (years)			
19–39	1 (Ref.)	1 (Ref.)	1 (Ref.)
40–59	0.51 (0.45–0.59)***	0.95 (0.66–1.38)	0.60 (0.50–0.71***
60–69	0.40 (0.32–0.51)***	0.76 (0.43–1.36)	0.49 (0.38–0.62***
70+	0.43 (0.33–0.56)***	0.68 (0.32–1.47)	0.46 (0.33–0.64)***
Obesity			
No (BMI<25.0)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes (BMI≥25.0)	1.03 (0.91–1.16)	1.15 (0.80–1.65)	1.21 (1.04–1.42)*
Smoking status			
Never smoker	1 (Ref.)	1 (Ref.)	1 (Ref.)
Ex-smoker	1.42 (1.15–1.75)***	0.78 (0.42–1.44)	1.32 (1.01–1.72)*
Smoker	2.01 (1.67–2.41)***	1.44 (0.88–2.36)	2.06 (1.65–2.57)***
Exercise			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	1.08 (0.95–1.24)	1.24 (0.79–1.94)	0.88 (0.74–1.04)
Social activity			
No	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	0.62 (0.55–0.70)***	0.39 (0.28–0.55)***	0.52 (0.45–0.60)***
Family income level			
1st quantile	1 (Ref.)	1 (Ref.)	1 (Ref.)
2nd quantile	0.73 (0.61–0.88)***	0.92 (0.59–1.43)	0.61 (0.48–0.76)***
3rd quantile	0.50 (0.42–0.59)***	0.35 (0.21–0.59)***	0.56 (0.46–0.68)***
4th quantile	0.45 (0.38–0.53)***	0.49 (0.30–0.81)**	0.47 (0.38–0.58)***
Educational level			
None	1 (Ref.)	1 (Ref.)	1 (Ref.)
Primary	0.69 (0.52–0.90)**	0.92 (0.47–1.82)	0.99 (0.71–1.38)
Secondary	0.54 (0.41–0.71)***	0.71 (0.33–1.55)	0.77 (0.54–1.09)
Tertiary	0.42 (0.31–0.56)***	0.66 (0.28–1.57)	0.53 (0.36–0.78)***
Occupation			
Manager/professional	1 (Ref.)	1 (Ref.)	1 (Ref.)
Clerical	0.74 (0.58–0.94)*	0.45 (0.18–1.16)	1.03 (0.77–1.37)
Service/sales	0.93 (0.75–1.15)	0.56 (0.28–1.12)	1.16 (0.87–1.53)
Agricultural/forestry/fishery	0.48 (0.35–0.66)***	0.35 (0.16–0.77)**	0.62 (0.43–0.89)**
Technician/operator	0.74 (0.59–0.92)**	0.70 (0.36–1.35)	0.89 (0.67–1.18)
House-wife	1.01 (0.82–1.25)	0.81 (0.43–1.54)	1.27 (0.97–1.66)
Unemployed	1.67 (1.33–2.08)***	0.71 (0.36–1.38)	1.64 (1.24–2.17)***
Others	0.55 (0.40–0.76)***	0.56 (0.20–1.55)	0.79 (0.51–1.21)

† OR adjusted for sex, age, obesity, smoking status, exercise, social activity, family income level, educational level, and occupation.

Abbreviation: AOR, adjusted odds ratio; CI, confidence interval; Ref, reference; BMI, body mass index. Level of statistical significance *<0.05, **<0.01, ***<0.001.

The second hypothesis was tested by calculating RERI and its 95% CI. A total of 133,178 participants were considered in the following analyses. Different cut-lines of alcohol intake (5 g/day, 15 g/day, 30 g/day) were set for three different analyses, and for each analysis, four subgroups were created. The reference groups for each analysis were (1) never flushing participants who drink less than 5 g/day, (2) never flushing participants who drink less than 15 g/day, and (3) never flushing participants who drink less than 30 g/day.

The result in Table 11 shows that the RERI is positive when the cut-line of alcohol intake was set as 5 g/day, while it is negative when the cut-line was set as 15 g/day or 30 g/day. Nevertheless, none of the values calculated here is statistically significant.

Table 11. Additive interaction of alcohol intake and alcohol flushing response

Alcohol intake (g/day)	Alcohol flushing response	Estimates (95% CI)	
		OR†	AOR‡
<5	Never flushing	1 (Ref.)	1 (Ref.)
	Current flushing	1.15 (1.03−1.29)*	1.20 (1.07−1.35)**
≥5	Never flushing	1.04 (0.93−1.16)	1.26 (1.12−1.43)***
	Current flushing	1.29 (1.12−1.49)***	1.56 (1.33−1.82)***
RERI		0.10 (−0.12−0.32) P=0.366	0.10 (−0.16−0.35) P=0.486
<15	Never flushing	1 (Ref.)	1 (Ref.)
	Current flushing	1.20 (1.09−1.33)***	1.23 (1.11−1.36)***
≥15	Never flushing	1.20 (1.06−1.36)**	1.46 (1.27−1.68)***
	Current flushing	1.35 (1.11−1.65)**	1.59 (1.29−1.97)***
RERI		−0.05 (−0.36−0.27) P=0.761	−0.1 (−0.47−0.28) P=0.609
<30	Never flushing	1 (Ref.)	1 (Ref.)
	Current flushing	1.21 (1.10−1.32)***	1.21 (1.10−1.33)***
≥30	Never flushing	1.65 (1.38−1.98)***	1.96 (1.61−2.37)***
	Current flushing	1.66 (1.26−2.19)***	1.90 (1.42−2.53)***
RERI		−0.20 (−0.75−0.34) P=0.467	−0.27 (−0.92−0.37) P=0.402

† OR of depression without any adjustments of the confounders.
‡ OR adjusted for sex, age, obesity, smoking status, exercise, social activity, family income level, educational level, and occupation.
Abbreviation: RERI, relative excess risk due to interaction; CI, confidence interval; Ref, reference; P, p−value. Level of statistical significance *<0.05, **<0.01, ***<0.001 .
Former flushers (n=6,107) were excluded in this analysis,

Chapter 4. Discussion

In a large community sample of Korean individuals, first the prevalence of the population who experience alcohol flushing response after a small amount of alcohol intake was investigated. The results showed that more than one-third of the current drinkers are current flushers and around two-fifth of the current drinkers were either current or former flushers. Second, the relationship between the response and depression among current drinkers was explored. A significant link between the current flushing response and depression was shown, with an adjusted OR of 1.19 (1.08-1.30), but there were no statistically significant odds of depression for former flushers. Third, a possible contributor, amount of alcohol intake, for the association between the flushing response and depression were explored. The result showed that the threshold of alcohol induced depression among current flushers was lower than never flushers.

Points regarding the prevalence and the characteristics of the alcohol flushing population correspond with the previous studies. The general prevalence of the alcohol flushing population was within the range of the other studies that 36 to 45 per cent of East Asians experience the alcohol flushing response. Furthermore, the association between the flushing response and depression is consistent with the findings of a recent study that ALDH2*2 heterozygotes have the highest odds for depression compared to

the other groups with lower alcohol sensitivity (Yoshimasu et al., 2016). Our study was able to support this study through a larger sample of the general population. While the former study had 25 subjects with depression among total study participants (n=602) and 12 subjects with depression among the group with a genotype that reveals flushing response (ALDH2*1/*2 and ALDH2*2/*2), the current study solely had 1,207 subjects with depression among 46,442 current flushers.

Several studies claim that people with inactive ALDH2 are protected from alcohol-associated risks since they have a greater tendency to abstain from drinking (Crabb et al., 2004). A research group concluded that the homozygotes of inactive ALDH2 are less likely to develop alcohol use disorders (AUD) as they refrain from consuming alcohol, and therefore, they will be less likely to develop depression related to AUD (Yoshimasu, 2015 a). Consequently, these study results could be interpreted that alcohol flushers, with inactive ALDH2, are protected from alcohol related to depression. In fact, the result of this study shows that alcohol flushers tend to drink less than never flushers. The current flushers generally drank less both in frequency and quantity-wise compared to the never flushers. Nevertheless, the current study result shows that alcohol flushers have a lower threshold to alcohol induced depression than never flushers. While the depression risk increased among never flushers who drinks more than 15 grams of alcohol per day (15-29.9 g/day: AOR=1.28, 95% CI=1.07-1.53, above 30 g/day:

AOR=2.21, 95% CI=1.79−2.73), the risk increased among current flushers who drinks more than 5 grams of alcohol per day and above 30 grams of alcohol per day (5−14.9 g/day: AOR=1.25, 95% CI=1.03−1.52; above 30g/day: AOR=1.64, 95% CI=1.01−2.21). Therefore, even though alcohol flushers have a tendency to drink less compared to never flushers, they can be more vulnerable to alcohol induced depression even with a small amount of alcohol. Like other health outcomes associated with alcohol drinking among alcohol flushers, alcohol flushers could be more vulnerable to the mechanism of acetaldehyde contributing to causing depressive states with a smaller dose of alcohol (Brancato et al., 2017).

A recent study (Zhu et al., 2020) suggested contrary results from Mendelian randomization (MR) of 476 middle−aged and older adults (average age: 49.4 years) in China; a protective effect of alcohol use was found for depression. Often, MR studies are perceived superior to observational studies, as the genetic variants employed as instrumental variables are inherited and not affected by confounders. Yet, estimates from MR studies must not always be interpreted as unbiased evidence of causality, as they may differ by subgroups (Salva & Neeland, 2018). The authors of the MR study on alcohol use and depression (Zhu et al., 2020) also reported studies on alcohol use and depression yielded different results according to country, the average age of the study population, and the definition of alcohol use/consumption, even in a study employing the MR framework. For example, a study conducted in Australia on

elderly male participants found no significant effect of alcohol consumption on depression, even with the use of an ADH1B genetic polymorphism as an instrumental variable (Almeida et al., 2014). Further, genetic variants that do not adequately explain the variation in the exposure may also provide biased causal estimates (Salva & Neeland, 2018). Large sample size is considered one of the partial solutions to the problem, yet a sample size of less than 500 may lack power. While instrument variable estimators could not be used in this study, our results were derived from a large, general population of 132,955 current drinkers. Thus, we conclude alcohol flushing serves as a useful and significant marker for predicting depression among drinkers in the Korean population aged 19 or more. Of course, further studies, perhaps one using MR framework on the general population, are required to generalize the relationship between alcohol use and depression.

The result of this study should be interpreted with caution due to the limitations listed as the following. First, although alcohol flushing response is a well-known proxy for inactive ALDH2, its characteristics cannot be completely equivalent to the characteristics of inactive ALDH2 genotype. Contrary to the characteristic of inactive ALDH2, where ALDH2*2/*2 homozygotes are unable to drink significant amounts of alcohol, numbers of flushing individuals of this study were found to drink above 30 grams of alcohol per day.

Second, this study does not cover the biochemical mechanisms

underlying the relationship between alcohol flushing response and depression. Thus, we encourage further studies to support our findings through the explanations of the mechanisms.

Third, since the analysis of this study was done with a secondary source of a cross-sectional study there are some restrictions in interpreting the study result. Variables such as alcohol intake would be a value measured during an intermediate course of one's life. Besides, unmeasured confounders could exist, although the confounders that could possibly influence the relationship between alcohol flushing response and depression were adjusted. For instance, the menstruation period or menopausal state among female participants may have influenced the survey result of depression. It is well known that cycling women experiences higher negative mood levels during menstruation than the other instances (Sutker, 1983). Women who had no history of depression are two to four times more likely to report depressed mood compared with premenopausal women, and women with a history of depression are nearly five times more likely to have a diagnosis of major depression in the menopausal transition (Freeman, 2010). These indicators, however, has been elusive in KCHS 2019. Therefore, we encourage further studies to control for the variables that were not sufficiently adjusted in this study.

Chapter 5. Conclusion

This study was conducted among a large community sample of Korean current drinkers. The prevalence of the alcohol flushing population, their characteristics, and the relationship between the response and depression was investigated. As a result, a significant number of Korean drinkers were alcohol flushers, and they were significantly more likely to develop depression at a lower level of alcohol consumption. These results indicate that current flushers may have a lower threshold to alcohol compared to never flushers, and that they are more likely to be depressed even though they are less likely to drink alcohol excessively.

The exploration of flushing population with a large sample group was a meaningful process. Unlike previous studies that identified the prevalence of the flushing group with a relatively small number of subjects, the results of this study can represent the actual population better. This study helps in clarifying the distribution of alcohol flushing response among the drinkers in Korean population, and help strengthening the evidence for underlying the relationship between alcohol and depression.

All in all, evidence from this study would provide a guideline for further studies regarding the flushing response and depression, and contribute to community-based intervention activities. For instance, clinicians, counsellors, or health professionals could inform alcohol flushing individuals of their risk of depression from alcohol drinking.

Furthermore, alcohol flushing response could be utilized as an indicator for predicting depression, and thus providing interventions for vulnerable individuals.

Bibliography

Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J., & Flicker, L. (2014). The triangular association of ADH1B genetic polymorphism, alcohol consumption and the risk of depression in older men. Molecular Psychiatry, 19(9), 995-1000.

Andrici, J., Hu, S. X., & Eslick, G. D. (2016). Facial flushing response to alcohol and the risk of esophageal squamous cell carcinoma: a comprehensive systematic review and meta-analysis. Cancer epidemiology, 40, 31-38.

Andrici, J., Hu, S. X., & Eslick, G. D. (2016). Facial flushing response to alcohol and the risk of esophageal squamous cell carcinoma: a comprehensive systematic review and meta-analysis. Cancer epidemiology, 40, 31-38.

Boccia, S., Hashibe, M., Gallì, P., De Feo, E., Asakage, T., Hashimoto, T., ... & Boffetta, P. (2009). Aldehyde dehydrogenase 2 and head and neck cancer: a meta-analysis implementing a Mendelian randomization approach. Cancer Epidemiology and Prevention Biomarkers, 18(1), 248-254.

Boden, J. M., & Fergusson, D. M. (2011). Alcohol and depression. Addiction, 106(5), 906-914.

Brancato, A., Lavanco, G., Cavallaro, A., Plescia, F., & Cannizzaro, C. (2017). Acetaldehyde, motivation and stress: behavioral evidence of an addictive ménage à trois. Frontiers in behavioral neuroscience, 11, 23.

Brooks, P. J., Enoch, M. A., Goldman, D., Li, T. K., & Yokoyama, A. (2009). The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. PLoS Med, 6(3), e1000050.

Crabb, D. W., Edenberg, H. J., Bosron, W. F., & Li, T. K. (1989). Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2 (2) allele is dominant. The Journal of clinical investigation, 83(1), 314-316.

Crabb, D. W., Matsumoto, M., Chang, D., & You, M. (2004). Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genesis of alcohol-related pathology. Proceedings of the nutrition society, 63(1), 49-63.

Enoch, M. A. (2014). Genetic influences on response to alcohol and response to pharmacotherapies for alcoholism. Pharmacology Biochemistry and Behavior, 123, 17-24.

Freeman, E. W. (2010). Associations of depression with the transition to menopause. Menopause, 17(4), 823-827.

Greenfield, T. K., & Kerr, W. C. (2008). Alcohol measurement methodology in epidemiology: recent advances and opportunities. Addiction, 103(7), 1082-1099

Hosmer, D. W., & Lemeshow, S. (1992). Confidence interval estimation of interaction. Epidemiology, 452-456.

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., ... & Briggs, A. M. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet, 392(10159), 1789-1858.

Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., & Lyu, J. (2020). Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. Journal of psychiatric research, 126, 134-140.

Manninen, L., Poikolainen, K., Vartiainen, E., & Laatikainen, T. (2006). Heavy drinking occasions and depression. Alcohol and alcoholism, 41(3), 293-299.

Mizoi, Y., Ijiri, I., Tatsuno, Y., Kijima, T., Fujiwara, S., Adachi, J., & Hishida, S. (1979). Relationship between facial flushing and blood acetaldehyde levels after alcohol intake. Pharmacology Biochemistry and Behavior, 10(2), 303-311.

Ota, M., Hisada, A., Lu, X., Nakashita, C., Masuda, S., & Katoh, T. (2016). Associations between aldehyde dehydrogenase 2 (ALDH2) genetic polymorphisms, drinking status, and hypertension risk in Japanese adult male workers: a case–control study. Environmental health and preventive medicine, 21(1), 1-8.

Pietraszek, M. H., Urano, T., Sumioshi, K., Serizawa, K., Takahashi, S., Takada, Y., & Takada, A. (1991). Alcohol-induced depression: involvement of serotonin. Alcohol and Alcoholism, 26(2), 155-159.

Savla, J., & Neeland, I. J. (2018). The Pros and Cons of Mendelian Randomization Studies to Evaluate Emerging Cardiovascular Risk Factors. Current Cardiovascular Risk Reports, 12(1), 1-9.

Shin, C. M., Kim, N., Cho, S. I., Sung, J., & Lee, H. J. (2018). Validation of alcohol flushing questionnaires in determining inactive aldehyde dehydrogenase-2 and its clinical implication in alcohol-related diseases. Alcoholism: Clinical and Experimental Research, 42(2), 387-396.

Shin, M. J., Cho, Y., & Smith, G. D. (2017). Alcohol consumption, aldehyde dehydrogenase 2 gene polymorphisms, and cardiovascular health in Korea. Yonsei medical journal, 58(4), 689.

Son, A. R., & Lee, S. S. (2009). 음주에 대한 가치, 태도, 음주문화에 대한 연구. In Proceedings of The Korean Society of Health Promotion Conference (pp. 259-260). Korean Society for Health Education and

Promotion.

Sutker, P. B., Tabakoff, B., Goist Jr, K. C., & Randall, C. L. (1983). Acute alcohol intoxication, mood states and alcohol metabolism in women and men. Pharmacology Biochemistry and Behavior, 18, 349-354.

Taylor, A. E., Lu, F., Carslake, D., Hu, Z., Qian, Y., Liu, S., ... & Smith, G. D. (2015). Exploring causal associations of alcohol with cardiovascular and metabolic risk factors in a Chinese population using Mendelian randomization analysis. Scientific reports, 5(1), 1-6.

VanderWeele, T. J., & Knol, M. J. (2014). A tutorial on interaction. Epidemiologic Methods, 3(1), 33-72.

Vos, T., Lim, S. S., Abbafati, C., Abbas, K. M., Abbasi, M., Abbasifard, M., ... & Bhutta, Z. A. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet, 396(10258), 1204-1222.

World Health Organization. Depression. World Health Organization, www.who.int/news-room/fact-sheets/detail/depression.

Yokoyama, A., Tsutsumi, E., Imazeki, H., Suwa, Y., Nakamura, C., Mizukami, T., & Yokoyama, T. (2008). Salivary acetaldehyde concentration according to alcoholic beverage consumed and aldehyde dehydrogenase-2 genotype. Alcoholism: Clinical and Experimental Research, 32(9), 1607-1614.

Yoshimasu, K., Mure, K., Hashimoto, M., Takemura, S., Tsuno, K., Hayashida, M., ... & Miyashita, K. (2015 a). Genetic alcohol sensitivity regulated by ALDH2 and ADH1B polymorphisms as indicator of mental disorders in Japanese employees. Alcohol and Alcoholism, 50(1), 39-45.

Yoshimasu, K., Mure, K., Hashimoto, M., Takemura, S., Tsuno, K.,

Hayashida, M., ... & Miyashita, K. (2015 b). Genetic alcohol sensitivity regulated by ALDH2 and ADH1B polymorphisms is strongly associated with depression and anxiety in Japanese employees. Drug and alcohol dependence, 147, 130-136.

Yoshimasu, K., Takemura, S., Tsuno, K., Hayashida, M., Kinoshita, K., Mure, K., ... & Miyashita, K. (2016). Depression, Alcoholism, and Genetic Alcohol Sensitivity Regulated by ALDH2 and ADH1B Polymorphisms among Japanese Community-Dwelling Adults. Archives of Depression and Anxiety, 2(1), 037-043.

Zhu, C., Chen, Q., Si, W., Li, Y., Chen, G., & Zhao, Q. (2020). Alcohol use and depression: a Mendelian randomization study from China. Frontiers in genetics, 11, 1286.

김명순, & 김광기. (2004). 직업관련 특성이 여성의 음주소비에 미친 영향. 보건교육건강증진학회지, 21(1), 1-23.

보건복지부. (2018). 음주폐해예방 실행계획.

오재환. (2002). 한국인의 여가와 음주문화. *사회연구*, *10*, 68-94.

인크루트. (2016). 술 강권하는 사회, 여러분의 술자리는 어떻습니까?. 인크루트. https://info.incruit.com/pr/report_view.asp?newsno=2679406

트렌드모니터. (2020). 감정노동과 스트레스 주는 직장 내 '회식 문화', 가급적 피하고 싶은 마음 뚜렷해. 엠프레인 컨텐츠사업부. http://www.openads.co.kr/content/contentDetail?contsId=4349

요약 (국문 초록)

알코올 홍조 반응과 우울증의 관계

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배경: 비활성 ALDH2의 생체지표이자 음주 후 안면 홍조나 매스꺼움 혹은 심박 급속증과 같은 증상을 동반하는 알코올 홍조 반응은 한국을 포함한 동아시아 집단의 1/3 이상에게서 나타나는 증상임에도 아직 국내 홍조군에 대한 전반적인 분포가 파악된 바가 없다. ALDH2는 알코올에서 유래되는 독성 물질인 아세트알데히드의 분해를 담당하는데, 비활성 ALDH2는 아세트알데히드의 대사를 저해하여 체내 축적을 일으키게 된다. 그 결과, 홍조군은 같은 양의 음주를 하더라도 비홍조군에 비해서 음주 관련 질환의 발생 위험에 차이가 있을 가능성이 있고, 특히 알코올과 밀접한 연관성이 있는 우울증과도 이러한 차이가 발견되는지는 아직 연구가 부족한 실정이다. 따라서, 본 연구는 일반 인구조사 결과를 통해서 국내 홍조군의 분포를 파악하고, 알코올 홍조와 우울증-위험의 연관성을 파악하고, 만약 관계가 있다면 그 이유를 유추하고자는 목적을 가진다.

연구 방법: 본 연구는 2019년에 시행된 지역사회건강조사(KCHS) 단면연구를 활용하여 분석을 진행했다. 연구 대상자는 총 139,285명으로 현재 음주자로 구성했다. 우울증 평가 도구(PHQ-9)를 통해서 대상자의 우울감의 여부와 심각도를 파악하여 총점이 10점

이상인 사람은 우울증이 있는 것으로 설정했고, 알코올 홍조 설문을 통해서 대상자의 알코올 홍조 상태를 파악하여 알코올 홍조 반응이 현재 있는 사람(현재 홍조군), 과거에 알코올 홍조 반응이 있었던 사람(과거 홍조군), 평생 홍조 반응이 없는 사람(비홍조군)으로 나누어 분석을 실시했다. 알코올 홍조 상태의 분포를 파악하기 위해서 대상자의 수는 가중치를 부여하지 않았고, 대상자의 분율은 가중치를 부여하여 계산했다. 로지스틱 회귀분석으로 알코올 홍조 상태에 따른 우울증의 관련성을 분석했다. 알코올 홍조 상태와 우울증 위험의 관계가 나타나는 이유를 찾기 위하여 층화분석과 상호작용 분석을 시행했다. 이 두 분석에서 보정한 혼란 변수는 성별, 나이, 흡연 여부, 신체활동 여부, 사회활동 참여여부, 가구 소득, 교육수준, 직업, 일별 음주량이고, 상호작용 분석에서는 과거 홍조군 6,107명을 제외하여 분석을 진행했다.

결과: 전체 연구 대상자의 약 60%가 비홍조군이었고, 35%가 현재 홍조군, 나머지 4% 정도가 과거 홍조군인 것으로 나타났다, 가중치를 부여한 우울증 유병율을 보면, 비홍조군 중 2.52%가 우울증이 있고, 과거 홍조군 중 2.63%, 현재 홍조군 중 2.93%가 우울증이 있는 것으로 나타났다. 과거 홍조 유무와 우울증은 유의한 상관성을 보이지 않았지만, 현재 홍조 유무와 우울증은 유의한 상관관계가 있는 것으로 나타났다(AOR=1.22, 95% CI=1.12−1.34). 홍조 상태에 따라서 층화분석을 시행할 결과 현재 홍조군은 비교적 적은 양의 음주를 했을 때부터 하루 5g 이하의 음주를 하는 사람에 비해서 우울증 위험이 유의하게 증가하는 것으로 나타났다(5−14.9 g/day: AOR=1.25, 95% CI=1.03−1.52; 30g/day 이상: AOR=1.64, 95% CI=1.01−2.21). 반면에 비 홍조군은 이보다 높은 양의 음주를 할 때 우울증 위험이 유의하게 증가하는 것으로 나타났다(15−29.9 g/day: AOR=1.28, 95%

CI=1.07−1.53); 30 g/day 이상: AOR=2.21, 95% CI=1.79−2.73). 음주량 자체는 우울증 위험을 증가시키는데 있어 홍조반응과 상호작용 효과가 없는 것으로 나타났다.

결론: 우리나라의 음주자 중에 상당수가 알코올 홍조 반응이 있는 것으로 나타났고, 이들에게서 우울 증상이 나타날 확률이 유의하게 높은 것으로 나타났다. 그리고, 홍조 반응이 있는 사람은 알코올에 대한 역치(threshold)가 낮아서 결국 적은 음주량에도 부정적인 영향을 받을 수 있고, 홍조군 중 전문행정관리직 이외의 직업을 가질 경우 우울증 위험이 증가할 수 있다. 따라서, 본 연구는 알코올 홍조 반응은 앞으로 국내 음주자의 우울증을 예측하는 지표로 활용하고 지역사회의 우울증 예방과 유병률을 낮추는 데 활용할 필요가 있음을 시사한다.

주요어: 알코올 홍조 반응, 비활성 ALDH2, 우울증, PHQ−9.

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