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Research Article

Depression, Alcoholism, and Genetic Alcohol Sensitivity Regulated by *ALDH2* and *ADH1B* Polymorphisms among Japanese Community-Dwelling Adults

Abstract

Background: Although strong association between drinking and depression as well as alcohol-related disorders (ARD) has been reported, the relationship between potential ability to drink (genetic alcohol sensitivity) and depression or ARD is unclear. Genetic alcohol sensitivity is regulated by two alcohol metabolic enzyme genes, *ADH1B* and *ALDH2* polymorphisms. We have already evaluated the association between depression and these polymorphisms in Japanese white-collar workers. Current study expanded this issue on community-dwelling relatively older adults.

Methods: A total of 654 community-dwelling people were interviewed regarding their ARD by a brief psychiatric structured interview (MINI). Severity of depression was evaluated by the Center for Epidemiologic Studies Depression Scale (CES-D). We investigated the relationship of *ADH1B* rs1229984 and *ALDH2* rs671 polymorphism combinations with depression and ARD risks. Logistic regression analysis was used to evaluate the associations between those polymorphisms and mental disorders, adjusting for sex, age, number of family members, physical exercise, job status, and serum lipid abnormality. The degree of alcohol sensitivity was classified into five groups according to the combination of two enzyme genotypes (Group I-V, in order from the lowest alcohol sensitivity).

Results: Those with *ALDH2* *1/*2 and *ADH1B* *1/*1 were likely to be at an increased risk of depression (OR 6.63, 95% CI 1.12-39.21). On the other hand, a genotype combination of *ALDH2* *1/*1 and *ADH1B* *1/*2 or *2/*2 was significantly associated with an increased risk of ARD (OR 3.93, 95% CI 1.86-8.31). Similar findings were observed when depression and ARD were combined as an outcome variable.

Conclusions: Genetic alcohol sensitivity with the genotype combination of *ALDH2* *1/*2 and *ADH1B* *1/*1 was significantly associated with an increased risk of depression, while Japanese community-dwellers in rural areas with *ALDH2* *1/*1 and *ADH1B* *1/*2 or *2/*2 were at a significantly elevated risk of ARD.

Abbreviations

ARD: Alcohol-Related Disorders; SNP: Single Nucleotide Polymorphisms; VNTR: Variable Number Of Tandem Repeat; MINI: Mini-International Neuropsychiatric Interview; CES-D: Center For Epidemiologic Studies Depression; PCR: Polymerase Chain Reaction; HWE: Hardy-Weinberg Equilibrium; ECG: Electrocardiogram; BMI: Body Mass Index; OR: Odds Ratio; CI: Confidence Interval; DSCF: Dwass, Steel, Critchlow-Fligner

Introduction

Abundant evidence has suggested that alcohol-related disorders (ARD; alcohol dependence/abuse) are accompanied by various other comorbid psychiatric disorders, especially internalizing disorders such as anxiety or depression [1-4]. While hard drinkers (i.e., those with low alcohol sensitivity) are likely to have any alcohol-related problem that can stem from ARD, leading to isolation from society and suffering from depression, those who have a "poor head for drink" (i.e., those with high alcohol sensitivity) cannot relieve their mental stress by moderate drinking, as moderate alcohol consumption has been shown to be effective for psychological stress reduction [5,6]. However, these 'drinking effects' depend on the social situations encountered by these people.

Community-based epidemiological studies have reported that weekly alcohol consumption was positively associated with brain atrophy [7], and that those with a higher quality diet were less likely to be depressed after adjustment for alcohol consumption [8]. These findings suggest that while habitual alcohol consumption by the elderly might have harmful effects on their brain function, those effects can be successfully compensated for by a lifestyle with a more healthful diet, which might be reflected as a different aspect on the association between drinking and mental health compared to white-collar workers.

Single nucleotide polymorphisms (SNPs) of the two enzymes' gene loci, *ADH1B* rs1229984 and *ALDH2* rs671 SNPs, which show different

alcohol/acetaldehyde oxidizing capabilities among individuals, have been reported to exert significant impacts on alcohol consumption and on the risk for ARD in East Asia populations [9-12].

Combining these two enzymes' polymorphisms, by which the velocity of accumulation and elimination of acetaldehyde is determined, degrees of alcohol sensitivity regulated by those enzymes' gene loci can be classified into the following five groups in order from the lowest alcohol sensitivity: Group I (*ALDH2 *1/*1* and *ADH1B *1/*1*), Group II (*ALDH2 *1/*1* and *ADH1B *1/*2,*2/*2*), Group III (*ALDH2 *1/*2* and *ADH1B *1/*1*), Group IV (*ALDH2 *1/*2* and *ADH1B *1/*2,*2/*2*), and Group V (*ALDH2 *2/*2* and *ADH1B *1/*1, *1/*2,*2/*2*) [13-16].

There is very little evidence regarding the combined effect of these two loci on internalizing mental disorders [17], in spite of the strong association found between them and ARD [1-4]. Most earlier studies on comorbidity between ARD and anxiety/depression have noted the genetic vulnerability of such internalizing disorders, and consequently focused on candidate genes such as *DRD2 Taq* A1, *CHRM2* SNPs 5'-UTR, *5-HTT* S-allele, *MAOA* promoter VNTR, and *SLC6A4* [3]. We have already reported that combination of these two enzymes' loci is associated with mental disorder risks [15], especially with depression and anxiety [16], in Japanese employees. However, as mentioned earlier, drinking habit and its associated mental problems are strongly affected by elements of demographic and socio-economic status, such as job or age. Our previous subjects were local government employees who were relatively young and bound by strict office regulation on drinking. Unfortunately, biomedical and lifestyle factors could not be controlled in those studies. However, these factors might play an important role on the association between drinking and mental health especially among community dwelling elderlies as mentioned above.

Thus, the purpose of the current study was to re-evaluate the associations between *ALDH2* and *ADH1B* polymorphisms and depression among relatively older people, almost half of whom had no job, and to confirm the reproducibility of our previous findings in that population with a sufficient adjustment of biomedical and lifestyle factors.

Methods

Sample

Our subjects were 1078 community-dwelling adults of two adjacent towns in the Kinki area of Japan who underwent annual health checkups from May to November 2014. They were mainly self-employed storekeepers or farmers, or unemployed (including housewives). Of the 1078 subjects investigators encouraged to enroll in the study, 654 (60.7%) agreed to participate in an interview survey regarding mental disorders, and provided blood samples to determine their two enzyme genetic polymorphisms. All participants gave written consent. This study was approved by the institutional review board for genetic research of Wakayama Medical University (acceptance number 106).

Assessment of alcohol-related disorders

The Mini-International Neuropsychiatric Interview (MINI), Japanese version 5.0.0 (2003) [18,19], a conveniently structured tool designed to identify mental disorders, was used for the present interview survey to confirm ARD. The reliability and validity of this tool were reported to be satisfactory [20]. A total of 12 interviewers, all of whom were licensed doctors or nurses except for one who was a kindergarten teacher, were considered competent to conduct the interviews, and were enrolled. The first author (K.Y.), a psychiatrist, trained all of them in essential interview skills, including didactic sessions of the general interview, and reviews of the instrument sections. Furthermore, the first author checked the interviewers and corrected them as the need arose during interview sessions so that the interviews could be conducted appropriately.

The screening question for ARD was as follows: 'In the past 12 months, have you had three or more alcoholic drinks within a three hour period on three or more occasions?' Three or more alcoholic drinks' in the Japanese version of the test means three or more glasses (three or more units on average) of any alcoholic beverage. A detailed interview was conducted on those who answered 'yes' to this screening question (i.e., drinkers) to confirm ARD as defined by DSM-IV and ICD-10. The detailed interview consisted of seven questions for alcohol dependence and four questions for alcohol abuse. Alcohol abuse was confirmed when subjects did not meet the criteria for alcohol dependence. Those with alcohol dependence or abuse were regarded as suffering from ARD.

Assessment of depression

Severity of depression was evaluated by the Center for Epidemiologic Studies Depression Scale (CES-D scale) [21]. This was administered to the subjects at the place of their annual health checkup. Those who had a score of 16 or more were regarded as suffering from depression. All missing values of MINI and CES-D were confirmed by a telephone interview on another day except for those who refused to participate, those who could not be reached by telephone, or whose telephone was broken.

Health checkup items

Annual health checkups were conducted for the community dwellers except for employees of a large-scale enterprise and their family members. Items of the checkups included a variety of medical examinations, such as electrocardiogram (ECG), body mass index (BMI), and lipid, hepatic, renal, urinary, and glucose metabolizing tests evaluated from blood and urine samples. From the results of these clinical examinations, if subjects needed daily observation, re-examination, detailed examination, or treatment or consultation with physicians, they were regarded as having an abnormality. Physicians of the hospital in charge of the health checkups made these medical decisions based on the tests results.

The self-administered questionnaire for the checkup included smoking and drinking habits, physical exercise, medications for hypertension, diabetes mellitus, and hyperlipidemia, as well as history of stroke, heart and renal diseases, and anemia. The questionnaire also confirmed a variety of subjective symptoms such as general fatigue, mental stress, abdominal pain, gastric discomfort, nausea/heartburn, constipation, hemorrhoids, feeling that something is wrong during evacuation, rapidly losing weight, thirst, headache/eyestrain/shoulder stiffness, giddiness, palpitation/getting out of

breath, chest pain, lumbago/back pain, cough/phlegm, numbness/arthralgia/edema, and disturbance of urination or hematuria. Those who had at least one symptom mentioned above were regarded as having any subjective symptoms.

Genetic analysis

Genetic determinations were made by examiners blinded to mental disorder status. All samples were directly genotyped by the TaqMan assay on an ABI 7300 Real Time PCR System [22].

Statistical analysis

The *p*-value for Hardy-Weinberg equilibrium (HWE) was calculated as the difference between the number of genotypes and the number of alleles (*df*=1). As for differences in demographic, socioeconomic, and biomedical factors among the five Groups, χ^2 test was used for categorical variables, and analysis of variance (ANOVA) was used for continuous variables.

Three statistical models were created for examining the associations between mental disorders and the two enzyme genetic polymorphisms, based on the definition of outcome variables. These outcomes were: (i) depression, (ii) ARD, and (iii) depression and ARD combined. Those who did not correspond to depression or ARD were categorized as normal controls (*N*=577).

Logistic regression analysis was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs). The dependent variables in that analysis were the three outcomes defined above, which were compared with the 577 controls. Explanatory variables were *ALDH2* and *ADH1B* genotypes classified as mentioned in the Introduction (Group I-V), adjusting for age and sex (model 1), and for age, sex, number of family members, physical exercise, employment status, and lipid abnormality, which showed statistically significant or nearly significant ($p<.10$) differences among the five Groups (model 2). Age was divided into two categories at the mean age.

The ORs and their 95% CIs were obtained from the corresponding logistic regression coefficients and their standard errors. Each OR showed how many times subjects with the genotypes were likely to have been affected by depression or ARD compared to Group IV. Group IV was set as the reference group since its members were considered better able to control their alcohol-related behaviors compared to the other lower sensitivity groups, as commonly seen in Japanese [14,23]. We also estimated trends of the OR in each model in accordance with the number of wild homozygotes found in the two loci.

In addition to multivariate logistic regression analysis, severity of depression was compared among the five Groups by non-parametric Kruskal-Wallis test followed by the Dwass, Steel, Critchlow-Fligner (DSCF) multiple comparison analysis. *P*-values (two-sided) less than 0.05 were considered statistically significant. All computations were performed using the SAS software package, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Distributions of demographic and job backgrounds of the subjects are shown in Table 1. Nearly 40% of the subjects were male and their mean age was 62, suggesting that the majority of the current sample were elderly. More than half of the participants were unemployed or housewives.

The distributions of *ALDH2* and *ADH1B* polymorphisms as well as their combined classification (Group I-Group V) among all samples are shown in Table 2. No significant deviation was detected by HWE among subjects, neither for *ALDH2* nor *ADH1B*. Group II was, as expected, the most frequent, followed by Group IV. Only nine members were categorized into Group III, the fewest among the five groups. These genotype distributions were consistent with previous Japanese studies [15,16,23].

Table 3 shows the differences in demographics and job background as well as results from the medical examination according to *ALDH2* and *ADH1B* polymorphism genotype classification. Groups III and V showed a relatively higher proportion of unemployed people

Table 1: Demographic and Job Backgrounds of Participants (*n*=654).

Variables	*n* (%)
Male	267 (40.8)
Age (mean±SD)	61.9±10.2
Number of family members[a] (mean±SD)	2.8±1.3
Job	
Unemployed[b]	364 (55.7)
Self-employed	117 (17.9)
Farmer	90 (13.8)
Salaried-employee	83 (12.7)

[a]Including the participant. [b]Including housewives.

Table 2: Frequencies of *ALDH2* and *ADH1B* Polymorphisms and Genotype Classification According to the Polymorphisms in Study Participants (*n*=654).

ALDH2 Glu487Lys (rs671,*1=G, *2=A)	*n* (%)
**1/*1*	350 (53.5)
**1/*2*	248 (37.9)
**2/*2*	56 (8.6)
HWE *p*-value	0.21
ADH1B Arg47His (rs1229984, *1=G, *2=A)	
**1/*1*	32 (4.9)
**1/*2*	239 (36.5)
**2/*2*	383 (58.6)
HWE *p*-value	0.50
Genotype Classification	
Group I (*ALDH2* *1/*1 and *ADH1B* *1/*1)	21 (3.2)
Group II (*ALDH2* *1/*1 and *ADH1B* *1/*2,*2/*2)	329 (50.3)
Group III (*ALDH2* *1/*2 and *ADH1B* *1/*1)	9 (1.4)
Group IV (*ALDH2* *1/*2 and *ADH1B* *1/*2,*2/*2)	239 (36.5)
Group V (*ALDH2* *2/*2 and *ADH1B* *1/*1, *1/*2,*2/*2)	56 (8.6)

HWE=Hardy-Weinberg Equilibrium.
Alcohol sensitivity: Group I & II: not sensitive, III: sensitive, IV: very sensitive, V: extremely sensitive.

Citation: Yoshimasu K, Takemura S, Tsuno K, Hayashida M, Kinoshita K, et al. (2016) Depression, Alcoholism, and Genetic Alcohol Sensitivity Regulated by ALDH2 and ADH1B Polymorphisms among Japanese Community-Dwelling Adults. Arch Depress Anxiety 2(1): 037-043. DOI: 10.17352/2455-5460.000013

Table 3: Demographics, Job Background, and Results of the Medical Examination, According to *ALDH2* and *ADH1B* Polymorphisms Genotype Classification.

Factors	Group I	Group II	Group III	Group IV	Group V	*p*-value[g]
Male (%)	28.6	39.8	22.2	43.1	44.6	0.47
Mean age (year)	58.5	62.0	58.1	62.9	58.9	0.027
Mean number of family members	3.5	2.6	2.8	2.9	3.1	0.003
Unemployed (%)	42.9	40.4	66.7	46.0	57.1	0.10
Drinkers[a] (%)	66.7	70.8	55.6	37.7	0.0	<.0001
Smokers[b] (%)	38.1	30.7	22.2	28.5	30.4	0.87
Physical exercise[c] (%)	28.6	37.1	0.0	34.3	25.0	0.082
Any subjective symptoms (%)	38.1	48.9	66.7	54.8	53.6	0.36
Any medications[d] (%)	42.9	39.8	22.2	40.6	37.5	0.84
ECG abnormality[e] (%)	23.8	19.5	0.0	21.8	19.6	0.57
BMI abnormality[e] (%)	0.0	2.1	0.0	3.4	5.4	0.55
Lipid abnormality[e] (%)	28.6	39.2	66.7	49.0	41.1	0.054
Hepatic abnormality[e] (%)	9.5	6.1	0.0	4.2	3.6	0.63
Renal abnormality[e h] (%)	10.5	15.8	11.1	19.2	18.0	0.76
Urinary abnormality[e] (%)	0.0	2.4	11.1	1.7	0.0	0.21
Glucose metabolizing abnormality[e] (%)	28.6	21.9	11.1	15.9	16.1	0.28
Anamnesis[f] (%)	14.3	18.2	11.1	19.3	19.6	0.95

[a] Occasional or daily drinker. [b] Past or current smoker. [c] Exercise once per week or more.
[d] Medications for hypertension, diabetes mellitus, and hyperlipidemia. [e] Abnormality that needs daily observation, re-examination, detail examination, or treatment or consultation with physician.
[f] History of stroke, heart disease, renal disease, or anemia. [g] χ^2 test for categorical variables; analysis of variance for continuous variables. [h] *n*=600. Housewives are included in the unemployed group.
Group I (*ALDH2 *1/*1* and *ADH1B *1/*1*) *n*=21; Group II (*ALDH2 *1/*1* and *ADH1B *1/*2,*2/*2*) *n*=329; Group III (*ALDH2 *1/*2* and *ADH1B *1/*1*) *n*=9; Group IV (*ALDH2 *1/*2* and *ADH1B *1/*2,*2/*2*) *n*=239; Group V (*ALDH2 *2/*2* and *ADH1B *1/*1, *1/*2,*2/*2*) *n*=56.
Alcohol sensitivity: Group I & II: not sensitive, III: sensitive, IV: very sensitive, V: extremely sensitive.

(*p*<.10). Mean age was likely to be low in Groups I and V, and greater numbers of family members were observed in those Groups with a statistical significance. Proportions of those who conducted physical exercise were likely to be higher in Groups II and IV. As for medical examinations, lipid abnormality was shown to be higher in Group III compared to the other Groups. No material differences were observed for other medical examinations among the five Groups. Proportions of drinkers were almost in accordance with the order of low alcohol sensitivity while those of smokers did not show any material differences among the Groups. Among daily drinkers (*N*=210), alcohol consumption per week per person (SD) was approximately calculated to be 197.6g (111.4) and significant difference was observed among the five groups by ANOVA (*P*=0.017). Members of Group I (*N*=9) had the highest average volume of alcohol consumption (243.6g).

The association between *ALDH2* and *ADH1B* polymorphisms according to their classification, and depression, was shown in Table 4. Group III was significantly associated with a more than six-fold increased risk of depression. Since there were no subjects with depression in Group I, calculation for this group could not be conducted.

Table 5 shows the association between Group I-V polymorphism classification and ARD. Group II showed a statistically significant association with an increased risk of ARD, and Group I was also likely to be associated with such a risk. Though Group III showed increased OR associated with ARD risk, this result should be interpreted with caution its 95% CI was too wide because only one subject had ARD.

The association between Group I-V polymorphism classification and depression/ARD combined was presented in Table 6. Group II was significantly associated with an increased risk of such disorders, while association between Group III and such disorders did not reach statistical significance due to few subjects being within that category. Group V was likely to be associated with a reduced risk of such disorders. Trends in associations between mental disorders and the two enzyme polymorphisms are shown in Table 7, according to the number of wild-homozygote genotypes in the two loci (0, 1, and 2). Significant trends for ARD and depression/ARD combined were observed (*p*=0.0006 and 0.0097, respectively).

Table 8 compares the severity of depression among the five Groups by Kruskal-Wallis test followed by DSCF multiple comparison analysis. The figures show median values since this test is non-parametric. Significant or nearly significant differences among the groups were observed in the entire sample and in drinkers who had three glasses of alcoholic drinks within a three-hour period on three or more occasions in the past year. Additional multiple comparisons showed that there were non-significant, modest differences between Group IV and Group V in the entire sample, and between Group I and Group II in drinkers.

Citation: *Yoshimasu K, Takemura S, Tsuno K, Hayashida M, Kinoshita K, et al. (2016) Depression, Alcoholism, and Genetic Alcohol Sensitivity Regulated by ALDH2 and ADH1B Polymorphisms among Japanese Community-Dwelling Adults. Arch Depress Anxiety 2(1): 037-043. DOI: 10.17352/2455-5460.000013*

Discussion

Regarding depression, the current study provided different findings from our previous studies which showed that Group I was most likely to be affected by mental disorder risks (14,15). Compared to Group IV (*ALDH2* *1/*2 and *ADH1B* *1/*2,*2/*2), who were considered to have self-inhibition against alcohol-related behaviors, Group III (*ALDH2* *1/*2 and *ADH1B* *1/*1) had the most elevated risk of depression while no subjects in Group I (*ALDH2* *1/*1 and *ADH1B* *1/*1) suffered from depression. On the other hand, Group II (*ALDH2* *1/*1 and *ADH1B* *1/*2,*2/*2) was at a significantly elevated risk for ARD as expected, and Group I was also likely to suffer from ARD, consistent with our previous findings. Although many of the wild-homozygote genotypes in the two loci (alleles related to low alcohol sensitivity) were significantly associated with ARD and depression/ARD combined, such a trend was not observed for depression only, which is also consistent with previous findings [16].

Thus, most apparent differences between current and previous findings are that Group III was most strongly associated with depression in the former study while Group I was in the latter. Because both groups had much fewer members compared to the other groups among the Japanese, the results related to these groups were strongly influenced by the number of affected cases within the groups. In the current study, there were no subjects with depression in Group I. On the other hand, there were too few subjects in Group III to conduct a sufficient multivariate analysis in the previous studies [15,16].

Table 4: Association Between *ALDH2* and *ADH1B* Polymorphisms and Depression (*n*=602).

	Number		Model 1[a]		Model 2[b]	
Groups	Cases	Controls	OR	95% CI	OR	95% CI
Group I	0	19	NA		NA	
Group II	13	276	1.15	0.48-2.75	1.14	0.47-2.77
Group III	2	7	6.10	1.07-34.83	6.63	1.12-39.21
Group IV	9	220	1.00	Ref	1.00	Ref
Group V	1	55	0.37	0.05-2.99	0.37	0.05-3.04

[a] Adjusted for sex and age.
[b] Adjusted for sex, age, number of family members, physical exercise, employment status, and serum lipid abnormality.
Case: those with CES-D score of 16 or more. NA=not available due to lack of subjects within the categories. Controls are
577 subjects without depression or alcohol-related disorders in both models.
Group I (*ALDH2* *1/*1 and *ADH1B* *1/*1); Group II (*ALDH2* *1/*1 and *ADH1B* *1/*2,*2/*2);
Group III (*ALDH2* *1/*2 and *ADH1B* *1/*1); Group IV (*ALDH2* *1/*2 and *ADH1B* *1/*2,*2/*2);
Group V (*ALDH2* *2/*2 and *ADH1B* *1/*1, *1/*2,*2/*2).
Alcohol sensitivity: Group I & II: not sensitive, III: sensitive, IV: very sensitive, V: extremely sensitive.

Table 5: Association Between *ALDH2* and *ADH1B* Polymorphisms and Alcohol-Related Disorders
(Alcohol Dependence and Abuse Combined, *n*=631).

	Number		Model 1[a]		Model 2[b]	
Groups	Cases	Controls	OR	95% CI	OR	95% CI
Group I	2	19	3.47	0.65-18.48	3.46	0.63-19.09
Group II	41	276	3.80	1.82-7.93	3.93	1.86-8.31
Group III	1	7	7.90	0.68-91.59	7.77	0.71-84.97
Group IV	10	220	1.00	Ref	1.00	Ref
Group V	0	55	NA		NA	

[a] Adjusted for sex and age.
[b] Adjusted for sex, age, number of family members, physical exercise, employment status, and serum lipid abnormality.
NA=not available due to lack of subjects within the categories.
Controls are 577 subjects without depression or alcohol-related disorders in both models.
Group I (*ALDH2* *1/*1 and *ADH1B* *1/*1); Group II (*ALDH2* *1/*1 and *ADH1B* *1/*2,*2/*2);
Group III (*ALDH2* *1/*2 and *ADH1B* *1/*1); Group IV (*ALDH2* *1/*2 and *ADH1B* *1/*2,*2/*2);
Group V (*ALDH2* *2/*2 and *ADH1B* *1/*1, *1/*2,*2/*2).
Alcohol sensitivity: Group I & II: not sensitive, III: sensitive, IV: very sensitive, V: extremely sensitive.

Table 6: Association Between *ALDH2* and *ADH1B* Polymorphisms and Depression and Alcohol-Related Disorders Combined (*n*=654).

	Number		Model 1[a]			Model 2[b]	
Groups	Cases	Controls	OR	95% CI		OR	95% CI
Group I	2	19	1.41	0.30-6.71		1.45	0.30-6.99
Group II	53	276	2.38	1.35-4.19		2.43	1.37-4.32
Group III	2	7	4.23	0.73-24.61		3.81	0.64-22.55
Group IV	19	220	1.00	Ref		1.00	Ref
Group V	1	55	0.18	0.02-1.39		0.19	0.02-1.45

[a] Adjusted for sex and age.
[b] Adjusted for sex, age, number of family members, physical exercise, employment status,
and serum lipid abnormality.
NA=not available due to lack of subjects within the categories.
Controls are 577 subjects without depression or alcohol-related disorders in both models.
Group I (*ALDH2* *1/*1 and *ADH1B* *1/*1); Group II (*ALDH2* *1/*1 and *ADH1B* *1/*2,*2/*2);
Group III (*ALDH2* *1/*2 and *ADH1B* *1/*1); Group IV (*ALDH2* *1/*2 and *ADH1B* *1/*2,*2/*2);
Group V (*ALDH2* *2/*2 and *ADH1B* *1/*1, *1/*2,*2/*2).
Alcohol sensitivity: Group I & II: not sensitive, III: sensitive, IV: very sensitive, V: extremely sensitive.

Table 7: Associations Between Number of *1/*1 in *ALDH2* and *ADH1B*, and Depression/Alcohol-Related Disorders in Subjects Except Group V.

	Model 1[a]		Model 2[b]		Model 3[c]	
Groups (*n* of *1/*1)	OR	95% CI	OR	95% CI	OR	95% CI
Group I (2)	NA		3.46	0.65-18.36	1.39	0.29-6.62
Group II+III (1)	1.28	0.55-3.01	3.84	1.84-8.01	2.41	1.37-4.24
Group IV (0)	1.00	Ref	1.00	Ref	1.00	Ref
p for trend	0.89		0.0006		0.0097	

[a] Outcome=Depression.
[b] Outcome=Alcohol-related disorders.
[c] Outcome=Depression and alcohol-related disorders.
Adjusted for age and sex.
NA=not available due to lack of subjects within the categories.
Group I (*ALDH2* *1/*1 and *ADH1B* *1/*1); Group II (*ALDH2* *1/*1 and *ADH1B* *1/*2,*2/*2);
Group III (*ALDH2* *1/*2 and *ADH1B* *1/*1); Group IV (*ALDH2* *1/*2 and *ADH1B* *1/*2,*2/*2);
Group V (*ALDH2* *2/*2 and *ADH1B* *1/*1, *1/*2,*2/*2).
Alcohol sensitivity: Group I & II: not sensitive, III: sensitive, IV: very sensitive, V: extremely sensitive.

Citation: *Yoshimasu K, Takemura S, Tsuno K, Hayashida M, Kinoshita K, et al. (2016) Depression, Alcoholism, and Genetic Alcohol Sensitivity Regulated by ALDH2 and ADH1B Polymorphisms among Japanese Community-Dwelling Adults. Arch Depress Anxiety 2(1): 037-043. DOI: 10.17352/2455-5460.000013*

In addition, the current subjects were basically elderly people, usually without jobs or self-employed, while the previous subjects were local government employees whose mean age was around 40, who had much different populations from the current samples. Group I of the current survey had a lower CES-D score compared to the other groups, suggesting that community-dwelling, self-employed or jobless people with low alcohol sensitivity (i.e., potentially strong drinkers) can relieve their mental strain by drinking, there being no strict regulations to prevent them.

On the other hand, unsatisfactory or inadequate drinking among such people in Group III might lead to frustration and mental distress since moderate alcohol consumption has been shown to be effective for psychological stress reduction as mentioned earlier [4,5,24], but those of Group III were considered not to eliminate all their mental stress by drinking. Interestingly, light or mild drinking was shown to be positively-associated with job satisfaction in males, indicating a clear hump-shaped relationship between life satisfaction and alcohol use [25]. Nobody in Group III conducted periodic physical exercise, and their proportion of lipid abnormality was highest among the five groups. In addition, Group III members had relatively few family members compared to the other groups. However, even after adjusting for these factors, the result did not change. Since both *ALDH2* and *ADH1B* were inactive in this group, alcohol or acetaldehyde remaining in the body might have had some negative influence on emotional brain function.

Table 8: Severity of Depression According to *ALDH2* and *ADH1B* Polymorphisms among Drinkers and Non-Drinkers.

	Group I	Group II	Group III	Group IV	Group V	*p*-value[c]
Entire sample						
CES-D score (median)	0	1	2	1	2	0.054
				$p = 0.13^d$		
Drinkers[a]						
CES-D score (median)	0	1	9.5	0	—	0.049
Drinkers[b]	$p = 0.11^d$					
CES-D score (median)	0.5	1	4	1	—	0.53
Non-drinkers[a]						
CES-D score (median)	1	1	2	1	2	0.41
Non-drinkers[b]						
CES-D score (median)	0	1.5	1	1	2	0.10

[a] Those who had three glasses of alcoholic drinks within a three-hour period on three or more occasions in the past year (drinkers) or did not (non-drinkers).
[b] Occasional or daily drinkers (drinkers) or not (non-drinkers).
[c] Kruskal-Wallis test.
[d] The Dwass, Steel, Critchlow-Fligner (DSCF) multiple comparison analysis was conducted to calculate *p*-values in combinations of two Groups out of the five Groups. Only *p*-values less than 0.20 between two Groups are shown.
Group I (*ALDH2* *1/*1* and *ADH1B* *1/*1*); Group II (*ALDH2* *1/*1* and *ADH1B* *1/*2,*2/*2*);
Group III (*ALDH2* *1/*2* and *ADH1B* *1/*1*); Group IV (*ALDH2* *1/*2* and *ADH1B* *1/*2,*2/*2*);
Group V (*ALDH2* *2/*2* and *ADH1B* *1/*1, *1/*2,*2/*2*).
Alcohol sensitivity: Group I & II: not sensitive, III: sensitive, IV: very sensitive, V: extremely sensitive.

As for the association between genetic alcohol sensitivity and lipid abnormality, recent Japanese study of alcoholic men revealed that *ADH1B*2* allele and *ALDH2* *1/*1* genotype were associated with an increased risk of the lipid abnormality (high serum triglyceride and low high-density-lipoprotein cholesterol [26], which is consistent with the current finding showing Group II and Group IV with high lipid abnormality. Although the proportion of lipid abnormality in Group III was highest among the five groups, there were very few subjects in Group III in the current study as described below.

Our previous studies showed that non-drinkers in Group I confronted a significantly elevated risk of mental disorders, including depression [15,16]. Because biomedical data were not available in those studies, the reason why Group I non-drinkers suffered from depression was unclear. However, some frustration stemming from abstinence, or strict office regulations or personal characteristics might explain these findings [15,16].

In brief, non-drinkers in Group I had a high proportion of depression as well as other mental disorders in the previous survey, with the highest risk of depressive disorders in that group (16). On the other hand, current subjects in Group I showed the lowest CES-D scores, suggesting that people with low alcohol sensitivity in a liberal environment are the least likely to suffer from depression. In such an environment, they can drink whenever and whatever they like. Therefore, we consider that the current findings are not inconsistent with the previous ones.

The results in this study should be interpreted according to their strengths and limitations. The strength of the current study is that data from medical health checkups were available and could be used as independent co-variables in the logistic regression analysis. On the one hand, potential limitations of the current survey are that there were very few subjects in Groups I and III, causing a failure to converge the regression model and leading to insufficient results from multivariate analysis. For example, regarding the analysis of ARD, the odds ratio of Group I was the same value as Group II, but did not reach a statistically significant level. Since both Groups I and III are very few in the East Asian population, it might be necessary to include more than 10,000 subjects to fully evaluate the associations between genotypes of these minor groups and mental disorder risks.

In conclusion, the current study demonstrated that alcohol sensitivity regulated by combinations of *ALDH2* and *ADH1B* polymorphisms may be a useful indicator of depression and alcohol-related disorders in community-dwelling adults. However, relations between mental disorders and *ALDH2* and *ADH1B* polymorphisms are likely to be affected by demographic and socioeconomic characteristics of the study populations. For example, factors such as developmental stage, individual characteristics including antisocial behavior, and environmental factors including culture, family environment and childhood adversity, have been found to influence the extent to which these polymorphisms affect a person's alcohol

involvement [27]. Further larger scale, cross-cultural, clinical or population-based studies undoubtedly will lead to a more thorough understanding of the role of gene polymorphisms related to alcohol metabolism in the development of depression and alcohol-related disorders, as well as other mental disorders.

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