Does the flushing response modify the relationship between alcohol intake and hypertension in the Japanese population? NIPPON DATA2010

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博士論文

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（飲酒と高血圧との関連はフラッシング反応により修飾されるか）

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ABSTRACT AND KEYWORDS

Background: The influence of alcohol intake on hypertension may vary depending on the flushing response, but this relationship has not been confirmed.

Objective: The relationship between alcohol intake and hypertension was examined according to the flushing response in a representative sample of the Japanese population.

Methods: Participants in the National Health and Nutrition Survey in 2010 were asked to participate in the baseline survey of NIPPON DATA2010. Here, we investigated the relationship between alcohol intake and hypertension according to the flushing response. Statistical analyses were performed in a cross-sectional manner using multiple logistic regression models after adjusting for age, body mass index, smoking status, present illness of diabetes mellitus, and present illness of dyslipidemia.

Results: Of the 1,139 men and 1,263 women, 659 and 463, respectively, had hypertension. Among the men, alcohol intake was positively associated with hypertension, regardless of the

flushing response (*P* for linear trend both < 0.05). This positive relationship was observed for both users and non-users of antihypertensive drugs. No interaction with the flushing response was observed (*P* for interaction = 0.360). In women, although the direction differed between flushers and non-flushers, the association between alcohol intake and hypertension was not significant, regardless of flushing response.

Conclusion: In Japanese men, alcohol intake was positively associated with hypertension in a manner that was not influenced by the flushing response. (222/250 words)

KEY WORDS:

Alcohol intake, Flushing response, Hypertension, NIPPON DATA2010

INTRODUCTION

Heavy alcohol intake is a known risk factor of hypertension.[1)] After alcohol intake, some people exhibit a flushing response (palpitations, shortness of breath, headaches, and/or facial flushing) because of the accumulation of acetaldehyde. Acetaldehyde, a toxic metabolite of alcohol, is oxidized in the mitochondria by aldehyde dehydrogenase (ALDH). ALDH, the second enzyme in the metabolic pathway, converts acetaldehyde to acetic acid and consists mainly of two isozymes (ALDH1 and ALDH2).[2)] ALDH2 has three genotypes: wild type ($ALDH2^1/2^1$), inactive heterozygote ($2^1/2^2$), and inactive homozygote ($2^2/2^2$). The ALDH2 genotype is determined by heredity; 37%-45% of Japanese individuals are inactive heterozygotes, while 7% are inactive homozygotes.[3)-5)] People who are inactive heterozygotes or inactive homozygotes tend to exhibit a flushing response.[3),6),7)] A simplified flushing questionnaire has been developed to predict the ALDH2 genotype.[8)]

Several studies have examined the relationship between alcohol intake and hypertension according to the flushing response.[9)-13)] However, the results have conflicted. Some studies have reported that the relationship between alcohol intake and hypertension differs by flushing response.[9),10)] On the other hand, several reports have concluded that the ALDH2 genotype does not modify the relationship between alcohol intake and hypertension or blood pressure (BP).[11)-13)] However, to our knowledge, there have been no reports examining alcohol intake and lack of BP control according to the flushing response.

Regarding the mechanism about the relationship between alcohol intake and hypertension according to the flushing response or ALDH2 genotype, the following mechanism was reported. Vasdev et al. hypothesized that alcohol-induced hypertension was caused vascular smooth muscle tonus due to increase of intracellular calcium, which has been associated with acetaldehyde on cell-membrane to calcium exchange in animal model.[14)-17),12)]

To investigate the relationship between alcohol intake and hypertension according to the flushing response in the general Japanese population, we performed a cross-sectional analysis according to sex in a representative Japanese sample, NIPPON DATA2010, consisting of subjects who participated in the National Health and Nutrition Survey of Japan.

METHODS

NIPPON DATA2010

National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged 2010 (NIPPON DATA2010) was created as a prospective cohort to study cardiovascular disease in 2010. The baseline survey was conducted as the National Health and Nutrition Survey of Japan in 2010 (NHNS2010), which was implemented by the Ministry of Health, Labour and Welfare of Japan. The details of NHNS2010 have been described elsewhere.[18)]

In November 2010, a total of 8,815 residents from 300 randomly selected districts throughout Japan participated in NHNS2010. Overall, 7,229 of the participants were over 20 years of age. Of these participants, 3,873 (men: 1,598; women: 2,275) completed the blood tests that were part of NHNS2010, and 2,898 participants (men: 1,239; women: 1,659)

subsequently agreed to participate in the baseline survey of NIPPON DATA2010 (response rate: 74.6%). The age distribution was similar between NIPPON DATA2010 participants and NHNS2010 participants (Table 1).[19] The baseline survey included an electrocardiography examination, blood tests, urinalysis and a questionnaire containing questions relevant to the study of cardiovascular disease. Trained researchers collected informed consent from the participants before they were enrolled.

The data from 7 persons could not be utilized, and these subjects were excluded. Finally, 2,891 participants (men: 1,236; women: 1655) were included in the analysis. The Institutional Review Board of Shiga University of Medical Science (No. 22-29, 2010) approved this study.

Study participants

In the main analysis, we examined the relationship between alcohol intake and

hypertension according to the flushing response. Of the 2,891 participants, we excluded 489 for the following reasons: self-reported ex-drinkers (n = 61), missing information (flushing response, alcohol intake, body mass index (BMI), smoking status, present illness of diabetes mellitus, and present illness of dyslipidemia and/or antihypertensive drug use) at baseline (n = 17), and never-drinkers (n = 411). We excluded ex-drinkers from the analysis because these individuals might have stopped drinking because of hypertension or some other chronic condition. We also excluded never-drinkers from the analysis because the questionnaire on flushing response could not be completed by individuals who had never drank. Overall, 2,402 participants (men: 1,139; women: 1,263) were included in the analyses.

Flushing response

We set the exposure as alcohol intake depending on the flushing response. We used a simplified flushing questionnaire to evaluate the flushing response.[8)] Yokoyama et al. reported

the validity of the simplified flushing questionnaire in Japanese. According to Yokoyama et al. , this simplified flushing questionnaire showed 90% sensitivity and 88% specificity in 610 Japanese men and 88% sensitivity and 92% specificity in 381 Japanese women when flushers were supposed to be inactive ALDH2.[20),21)]

The questionnaire consisted of two questions: (a) “Do you flush in the face immediately after drinking a glass of beer?” (possible answers: partly, entire face, no, or unknown) and (b) “Did you flush in the face immediately after drinking a glass of beer during the first to second year after you started drinking?” (possible answers: yes, no, or unknown).

We classified the participants into two groups according to their answers. Individuals who answered ‘partly’ or ‘entire face’ to question (a) were classified as ‘flushers.’ Furthermore, those who answered ‘no’ or ‘unknown’ to question (a) and ‘yes’ to question (b) were also classified as ‘flushers.’ The remaining subjects were classified as ‘non-flushers.’

Alcohol intake

Information on alcohol intake (frequency and amount per day) was ascertained using a self-reported questionnaire. The frequency of alcohol intake was classified into the following six categories: every day, 5-6 days/week, 3-4 days/week, 1-2 days/week, 1-3 days/month, and almost never. Alcohol intake was grouped into the following six categories: ≥5 *gou*/day, 4-5 *gou*/day, 3-4 *gou*/day, 2-3 *gou*/day, 1-2 *gou*/day, and <1 *gou*/day, where '*gou*' represented the traditional Japanese unit of sake. For sake, 1 *gou* (180 mL) is equivalent to 22.1 g of alcohol, which is roughly two single shots of whisky (70 mL) or one bottle of beer (633 mL). The average weekly alcohol intake (g/week) was calculated for each participant using data on the frequency and amount of alcohol intake. The average frequencies and amounts used for each category were as follows: for frequency, 7 days/week, 5.5 days/week, 3.5 days/week, 1.5 days/week, 0.5 days/week, and 0 days/week, and for amount, 5 *gou*/day (=110.5 g of ethanol), 4.5 *gou*/day (=99.5 g of ethanol), 3.5 *gou*/day (=77.4 g of ethanol), 2.5

gou/day (=55.3 g of ethanol), 1.5 *gou*/day (=33.2 g of ethanol), and 0.5 *gou*/day (=11.1 g of ethanol). For men, alcohol intake was classified into the following 4 categories: 0 g/week (equivalent to 0 *gou*/day), 0.0-154.6 g/week (equivalent to 0 < *gou*/day < 1), 154.7-309.3 g/week (equivalent to 1 ≤ *gou*/day < 2), and more than 309.4 g/week (equivalent to ≥2 *gou*/day). For women, alcohol intake was classified into the following 3 categories: 0 g/week (equivalent to 0 *gou*/day), 0.0-154.6 g/week (equivalent to 0 < *gou*/day < 1), and more than 154.7 g/week (equivalent to ≥1 *gou*/day).

BP measurement

BP was measured twice by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants. Hypertension was defined as a systolic BP (SBP) ≥140 mmHg and/or a diastolic BP (DBP) ≥90 mmHg and/or the use of antihypertensive drugs.[22)] The first measurement was obtained after the subject had rested in a

sitting position for at least five minutes. The average of the two measurements was used.

Statistical analysis

As the alcohol intake differed between the men and the women, the data were analyzed separately for men and for women throughout the analyses.

Regarding the characteristics of the subjects, we tested for trends in age, BP (continuous variables), proportion with obesity, smoking status, and use of antihypertensive drugs (categorical variables). All *P* values for linear trends were calculated using the categories of alcohol intake. Additionally, we tested for interactions to compare the characteristics of flushers and non-flushers. We used a general linear model for continuous variables and a logistic regression model for categorical variables.

Multiple logistic regression models with hypertension as a dependent variable were applied to the main analyses. We included possible confounding factors, such as age, BMI

(<18.5, 18.5-24.9 and ≥25.0 kg/m^2), smoking status (never-smoker, ex-smoker, and current smoker), present illness of diabetes mellitus (yes, no) and present illness of dyslipidemia (yes, no) in the adjusted models. Additionally, we tested for linear trends in BP according to the flushing response and for interactions between alcohol intake and the flushing response. *P* values for linear trends were calculated using the categories of alcohol intake. In the interaction term analysis, we included a cross-product term for alcohol intake and flushing response in the model.

To consider the influence of antihypertensive drugs, we stratified the participants into two groups: non-users (n=1,795) and users (n=607) of antihypertensive drugs. We performed an analysis of covariance to calculate the adjusted mean BP. A multiple logistic regression analysis was also conducted for each group. In the analyses, the dependent variable was the lack of BP control, which was defined as an SBP of ≥140 mmHg or a DBP of ≥90 mmHg. In both analyses, we included age, BMI, smoking status, present illness of diabetes mellitus and

present illness of dyslipidemia as potential confounding factors. Additionally, we tested for linear trends in hypertension or BP according to the flushing response and for interactions between alcohol intake and the flushing response. *P* values for linear trends were calculated using the categories of alcohol intake.

All *P* values were two-sided, and $P < 0.05$ was regarded as being statistically significant. All analyses were performed using SAS version 9.4 for Windows (SAS Inc, Cary, NC).

RESULTS

Table 2 shows the baseline characteristics of the participants according to alcohol intake and flushing response. Of the 1,139 men and 1,263 women, 583 (51.2%) and 597 (47.3%), respectively, were classified as flushers.

Among the men, BP increased with alcohol intake in both the flushers and the non-flushers. Similarly, the proportion of ex-smokers increased with alcohol intake among flushers, and the proportion of current smokers increased with alcohol intake among non-flushers. Meanwhile, the proportion of never-smokers decreased with alcohol intake among both flushers and non-flushers. Of the non-flushers, the non-drinkers were younger than the drinkers. We did not observe any interaction between the presence of flushing response and any of the variables that were examined.

Regarding women, individuals with a higher alcohol intake were more likely to be

younger. Furthermore, the BP did not increase with alcohol intake among non-flushers. In both non-flushing and flushing women, the proportion of ex-smokers increased with alcohol intake. The relationships between alcohol intake and age, BP, smoking status, and use of antihypertensive drugs differed according to the flushing response.

Table 3 shows the relationship between alcohol intake and hypertension according to the presence of flushing response. Of the 1,139 men and 1,263 women, 659 (57.9%) and 463 (36.7%), respectively, had hypertension. The prevalence of drinkers was 64%, 90%, 34%, and 58% among the male flushers, male non-flushers, female flushers, and female non-flushers, respectively. In men, the median alcohol intake was 16.6 g/week (Interquartile range (IQR):0.0, 182.3) in flushers and 149.2 g/week (IQR: 38.7, 232.1) in non-flushers, respectively. On the other hand, the median alcohol intake among flushers was 0.0 g/week (IQR: 0.0, 5.5) and 5.5 g/week (IQR: 0.0, 49.7) among non-flushers in women. The median alcohol intake was lower in flushers than in non-flushers regardless of sex.

Among men, alcohol intake was positively associated with hypertension in both flushers and non-flushers (*P* for linear trend both < 0.05). Of the flushers, the adjusted odds ratio (aOR) compared with the group with an alcohol intake of 0 *gou*/day was 1.10 (95% confidence interval [95% CI], 0.71-1.72) for 0 < *gou*/day < 1, 1.86 (95% CI, 1.07-3.23) for 1 ≤ *gou*/day < 2, and 1.91 (95% CI, 0.92-3.96) for 2 ≤ *gou*/day (*P* for linear trend = 0.016). Of the non-flushers, the aOR compared to the group with an alcohol intake of 0 *gou*/day was 1.28 (95% CI, 0.62-2.68) for 0 < *gou*/day < 1, 2.43 (95% CI, 1.14-5.17) for 1 ≤ *gou*/day < 2, and 2.62 (95% CI, 1.16-5.92) for 2 ≤ *gou*/day (*P* for linear trend = 0.001). We observed no interaction with the flushing response (*P* for interaction = 0.360). Among women, although the direction differed between flushers and non-flushers (*P* for interaction = 0.052), the association between alcohol intake and hypertension was not significant, regardless of the presence of a flushing response (*P* for linear trend > 0.05).

Table 4 shows the relationship between alcohol intake and hypertension according to

the flushing response in participants who did not take antihypertensive drugs. In men, alcohol intake was positively associated with hypertension regardless of flushing response (*P* for linear trend < 0.05). We observed no interaction with the flushing response (*P* for interaction > 0.05). Among women, the association between alcohol intake and hypertension was not statistically significant for flushers or non-flushers (*P* for linear trend > 0.05).

Table 5 shows the relationship between alcohol intake and lack of BP control (≥ 140/90 mmHg) according to the flushing response among participants taking antihypertensive drugs. In men, alcohol intake was positively associated with lack of BP control among flushers (*P* for linear trend = 0.007). Although the difference was not statistically significant (*P* for linear trend = 0.114), the aOR was higher in the ≥2 *gou*/day group than in the lower alcohol intake groups. We observed no interaction with the flushing response (*P* for interaction = 0.481). In women, the association between alcohol intake and a lack of BP control was not significant for flushers or non-flushers (*P* for linear trend > 0.05).

DISCUSSION

We examined the relationship between alcohol intake and hypertension according to flushing response using NIPPON DATA2010, which provided data from a representative Japanese population. For men, alcohol intake was positively associated with hypertension in flushers and non-flushers. The flushing response did not modify the relationship between alcohol intake and hypertension.

In this study, we decided to classify alcohol intake into 4 categories (0 *gou*/day, 1 ≤ *gou*/day < 2, 2 ≤*gou*/day) for men and 3 categories (0 *gou*/day, 0 < *gou*/day < 1, 1 ≤*gou*/day) for women. Because number of 2 ≤*gou*/day drinkers for men and 1 ≤*gou*/day drinkers for women are small. Additionally, we decided the number of categories in reference to previous studies and distribution of alcohol intake. Most previous studies treated alcohol intake as categorical variable. Only one previous study treated alcohol intake as continuous variable.[5)]

We additionally examined the relationship between alcohol intake and hypertension according to the flushing response treating alcohol intake as continuous variable. Accordingly, the result did not change essentially, and alcohol intake was positively associated with hypertension in flushers and non-flushers among men (data not shown). On the other hand, the result was similar among women when evaluated for alcohol intake as categorical variables. Although we observed interaction with the flushing response (P for interaction = 0.0497), the association between alcohol intake and hypertension was not significant, regardless of the presence of a flushing response (data not shown). Further studies are required to address this case.

In our study, the median alcohol intake was lower among flushers than among non-flushers regardless of sex. Flushers were likely to exhibit a flushing response. This could be explained by the fact that flushers had experienced the uncomfortable symptoms of the flushing response and were thus likely to stop or reduce their alcohol consumption.

For men, alcohol intake was positively associated with hypertension among both flushers and non-flushers. Our findings were consistent with the results of some studies. In a meta-analysis, male drinkers with a high alcohol intake (>50 g/day) had a higher risk of hypertension than non-drinkers (relative risk: 1.61, 95% CI: 1.38-1.87).[1] Ueshima et al.[23] also found that moderate or heavy alcohol intake was associated with BP and the presence of hypertension among men in Japan.

Regarding the interaction between alcohol intake and hypertension according to flushing response, several reports have shown that alcohol intake is associated with BP among subjects with an inactive ALDH2 genotype or among flushers, but not among individuals with an active ALDH2 genotype or non-flushers.[9),10),24),25] However, none of those studies presented a *P* for interaction. In those reports, the following mechanisms were considered. Jung et al.[25),26] hypothesized that the increased BP in flushers was caused by the release of noradrenaline due to sympathetic nerve stimulation to compensate for the reduction in

visceral blood flow resulting from peripheral vasodilation, which has been associated with poor acetaldehyde removal. The results of our study, however, do not support this mechanism.

We demonstrated that the flushing response did not modify the relationship between alcohol intake and hypertension among men. Our results agree with those from other studies.[11)-13),27)] Although the results of the statistical tests examining the interaction were not provided, Amamoto et al.[5)] and Okayama et al.[28)] also reported that the ALDH2 genotype did not modify the relationship between alcohol intake and hypertension or BP among men.

We considered several reasons for the discrepancy between our study and the previous studies mentioned above. First, the age groups differed. The mean ages were 53.3 years and 39.3 years in the studies by Nakagawa et al.[10)] and Itoh et al.[24)], respectively. In the study by Jung et al.[9)], the mean ages were 50.9 years, 49.2 years, and 48.7 years in the non-drinkers, flushers, and non-flushers, respectively. In comparison, the mean age in our study was older (57.1 years) than those in the other studies. Second, the prevalence of

hypertension differed between the studies. The prevalence of hypertension was 28% and 27% in the studies reported by Nakagawa et al.[10] and Itoh et al.[24], respectively. Meanwhile, in our study, the prevalence of hypertension was higher (47%) than those of the other studies. These differences in age and prevalence of hypertension may have influenced the discrepancy between the results of our study and those of the previous studies. Another possible reason for the discrepancy may be the categorization of the ex-drinkers. None of the previous studies clearly distinguished between never-drinkers and ex-drinkers among the non-drinkers. However, we excluded ex-drinkers from the present analyses. Ex-drinkers may have stopped consuming alcohol because they were suffering from a disease. If ex-drinkers had been included among the non-drinkers, the effect of alcohol consumption on hypertension would probably have been underestimated because the prevalence of hypertension would have likely increased among the non-drinkers in our study. Thus, we believed that our approach was appropriate to assess the association between alcohol intake and hypertension.

Among women, we found no statistically significant associations between alcohol intake and hypertension, regardless of flushing response. A meta-analysis[1)] performed in the United States reported that the risk of hypertension was significantly higher among female drinkers (31-40 g/day) than non-drinkers (OR: 1.19, 95% CI: 1.07-1.32). Marmot et al.[29)] reported a higher blood pressure in heavy drinkers than in non-drinkers among women. Thus, our results were inconsistent with these previous reports. Several possibilities might explain the lack of positive association between alcohol intake and hypertension in our study. First, women in Japan, especially older women, tend to not drink regardless of their flushing response. In fact, among the non-flushers, the mean age of the non-drinkers was higher. Because the mean age of the non-drinkers was higher, the BP among non-drinkers was also higher than that among those who drank ≥1 *gou* /day. Although we adjusted for age, we might not have been fully able to adjust for the effects of age. Second, the number of alcohol intake categories was relatively small. Marmot et al.[29)] reported that among women, the mean BP

was 3.9 (SBP)/3.1 (DBP) mmHg higher in the heavy alcohol intake group (≥34 g/day) than in the non-drinking group, and these differences were statistically significant. However, in our study, we could not perform a detailed categorization because the number of female drinkers was relatively small. Consequently, we were only able to define three alcohol intake groups, and this smaller number of female moderate/heavy drinkers may have also been responsible for the non-significant relationship between alcohol intake and hypertension in this study.

Since *P* values were two-sided, and $P< 0.05$ was regarded as being statistically significant, we concluded that there was no interaction between flushing response and alcohol intake for hypertension among women. If we used $P< 0.10$ as being statistically significant, the association between alcohol intake and hypertension would have differed by flushing response. However, neither relation between alcohol intake and hypertension among flusher nor that among non-flusher were statistically significant. Therefore, we considered that the suggested interaction did not have clinical significance. Further studies are needed to address

this topic in larger sample size.

Nutrient status might have some influence on the relationship between alcohol intake and hypertension. Therefore, we performed sub-analyses with a model putting sodium intake and energy as confounding factors. However, the result did not change (data not shown). Among men, alcohol intake was positively associated with hypertension in both flushers and non-flushers. Among women, the association between alcohol intake and hypertension was not significant, regardless of the presence of a flushing response. Consequently, we considered the result that alcohol intake was associated with hypertension to be robust.

In this study, we analyzed antihypertensive drug users and non-users separately. For men, we observed a positive relationship between alcohol intake and hypertension regardless of the use of antihypertensive drugs. With respect to the positive association in subjects who did not take antihypertensive drugs, our finding was consistent with the results reported by Wakabayashi et al. [30] They reported that among Japanese men ≥65 years old who did not take

antihypertensive drugs, the prevalence of a high SBP and a high DBP was significantly higher in excessive alcohol drinkers than in non-drinkers (OR of SBP ≥140 mmHg: 1.62, 95% CI: 1.18-2.23; OR of DBP ≥90 mmHg: 1.77, 95% CI: 1.10-2.85).

As for the positive relationship in subjects who were taking antihypertensive drugs, our finding was consistent with the results reported by Wagner et al.[31]. Wagner et al.[31] reported that the risk of a lack of BP control was significantly higher for heavy alcohol drinkers than for non-drinkers in French men aged 35-74 years old who were being treated for hypertension (OR: 2.25, 95% CI: 1.07-4.75). However, Wakabayashi et al.[30] reported conflicting results. They did not find a significant association between excessive alcohol intake and BP among subjects who were taking antihypertensive drugs (OR of SBP ≥140 mmHg: 1.29, 95% CI: 0.86-1.95; OR of DBP ≥90 mmHg: 0.93, 95% CI: 0.52-1.67). This discrepancy can be explained by the different age ranges of the participants. In our study, the participants were older than 20 years, and in the study reported by Wagner et al.[31], the

included subjects were aged 35-74 years; in contrast, the study reported by Wakabayashi et al.[30] was limited to men over the age of 65 years.

The positive relationship between drinking and hypertension among untreated subjects suggests that some biological mechanisms may be involved. On the other hand, the positive relationship between drinking and a lack of BP control among treated subjects suggests that drug compliance might be relatively poor among heavier drinkers. Because the present study and previous studies did not measure compliance to antihypertensive drugs, future studies that account for drug compliance would be helpful in improving our understanding of the relationship between alcohol intake and BP among treated subjects.

The present study had several strengths. First, our study participants were from the National Health and Nutrition Survey, which was conducted in 300 randomly selected districts across Japan in 2010. Therefore, our data were representative of current Japanese conditions. Second, to our knowledge, this is the first report to examine alcohol intake and a lack of BP control

according to flushing response among participants taking antihypertensive drugs. It is important to consider whether the association between alcohol intake and hypertension differs by the flushing response after excluding the influence of antihypertensive drugs. And also, it is important to know the influence of alcohol intake on poor BP control among participants taking antihypertensive drugs. To clarify these issues, stratification according antihypertensive drugs should be required. To our knowledge, this is the first study about alcohol intake and hypertension according to the flushing response stratified by use of antihypertensive drugs. Third, the present study targeted Japanese population which half of them were flushers. It allowed us to investigate the influence of flushing on the association between alcohol and hypertension, whereas it is difficult to conduct this kind of study outside Asia because about 100% of Caucasians and Africans have wild type of ALDH2 genotype.[32)] Finally, only a few study investigated regarding interaction of flushing response and alcohol intake on hypertension. Two of four previous studies which reported the relationship between alcohol

intake and hypertension differed by flushing response were conducted in Japan. However, they did not perform statistical tests examining the interaction of flushing response and alcohol intake on hypertension. Our study investigated the interaction of flushing response by statistical analysis.

Our study also had some limitations. First, as we did not directly determine the ALDH2 genotype, we could not classify the participants who had never drank as belonging to either the flusher or non-flusher group. Second, in our study, BP was measured at one occasion during the day. As alcohol intake has been positively associated with a morning surge in BP[33], assessing 24-hour BP might have clarified a more detailed association between alcohol consumption and hypertension according to the flushing response. Further studies are required to address this topic. Third, on the basis of the cross-sectional design, it is difficult to confirm causality in this study. Some participants may have abstained from alcohol drinking because of their hypertension. These participants would have been classified in the lower

alcohol categories. Accordingly, the effect of alcohol intake on hypertension may have been underestimated because of the higher estimated prevalence of hypertension in the lower alcohol intake categories. However, for men, alcohol intake was positively associated with hypertension among both flushers and non-flushers in this study. We believe that the association between alcohol intake and hypertension is robust. Finally, other potential confounding factors may have existed.

In conclusion, we found that alcohol intake was positively associated with hypertension among flushers and non-flushers without any interaction in Japanese men. In other words, a reduction in alcohol intake may be beneficial for BP reduction in both flushers and non-flushers.

CONFLICTS OF INTEREST:

The author declare no conflicts of interest.

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REFERENCES

1 Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. *J Clin hypertens* 2012; **14**: 792-798.

2 Greenfield NJ, Pietruszko R. Two aldehyde dehydrogenases from human liver. Isolation via affinity chromatography and characterization of the isozymes. *Biochim Biophys Acta* 1977; **483**: 35-45.

3 Takeshita T, Morimoto K, Mao X, Hashimoto T, Furuyama J. Characterization of the three genotypes of low Km aldehyde dehydrogenase in a Japanese population. *Hum Genet* 1994; **94**: 217-223.

4 Wakai K, Hamajima N, Okada R, Naito M, Morita E, Hishida A, Kawai S, Nishio K, Yin G, Asai Y, Matsuo K, Hosono S, Ito H, Watanabe M, Kawase T, Suzuki T, Tajima K, Tanaka K, Higaki Y, Hara M, Imaizumi T, Taguchi N, Nakamura K, Nanri H, Sakamoto T,

Horita M, Shinchi K, Kita Y, Turin TC, Rumana N, Matsui K, Miura K, Ueshima H, Takashima N, Nakamura Y, Suzuki S, Ando R, Hosono A, Imaeda N, Shibata K, Goto C, Hattori N, Fukatsu M, Yamada T, Tokudome S, Takezaki T, Niimura H, Hirasada K, Nakamura A, Tatebo M, Ogawa S, Tsunematsu N, Chiba S, Mikami H, Kono S, Ohnaka K, Takayanagi R, Watanabe Y, Ozaki E, Shigeta M, Kuriyama N, Yoshikawa A, Matsui D, Watanabe I, Inoue K, Ozasa K, Mitani S, Arisawa K, Uemura H, Hiyoshi M, Takami H, Yamaguchi M, Nakamoto M, Takeda H, Kubo M, Tanaka H. Profile of participants and genotype distributions of 108 polymorphisms in a cross-sectional study of associations of genotypes with lifestyle and clinical factors: a project in the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study. *J Epidemiol*. 2011; **21**: 223-235.

5 Amamoto K, Okamura T, Tamaki S, Kita Y, Tsujita Y, Kadowaki T, Nakamura Y, Ueshima H. Epidemiologic study of the association of low-Km mitochondrial acetaldehyde dehydrogenase genotypes with blood pressure level and the prevalence of hypertension in a

general population. *Hypertens Res* 2002; **25**: 857-864.

6 Harada S, Agarwal DP, Goedde HW. Aldehyde dehydrogenase deficiency as cause of facial flushing reaction to alcohol in Japanese. *Lancet* 1981; **2**: 982.

7 Mizoi Y, Ijiri I, Tatsuno Y, Kijima T, Fujiwara S, Adachi J, Hishida S. Relationship between facial flushing and blood acetaldehyde levels after alcohol intake. *Pharmacol Biochem Be* 1979; **10**: 303-311.

8 Yokoyama A, Muramatsu T, Ohmori T, Kumagai Y, Higuchi S, Ishii H. Reliability of a flushing questionnaire and the ethanol patch test in screening for inactive aldehyde dehydrogenase-2 and alcohol-related cancer risk. *Cancer Epidemiol Biomarkers Prev* 1997; **6**: 1105-1107.

9 Jung JG, Kim JS, Kim YS, Oh MK, Yoon SJ. Hypertension associated with alcohol consumption based on the facial flushing reaction to drinking. *Alcohol Clin Exp Res* 2014; **38**: 1020-1025.

10 Nakagawa T, Kajiwara A, Saruwatari J, Hamamoto A, Kaku W, Oniki K, Mihara S, Ogata Y, Nakagawa K. The combination of mitochondrial low enzyme-activity aldehyde dehydrogenase 2 allele and superoxide dismutase 2 genotypes increases the risk of hypertension in relation to alcohol consumption. *Pharmacogenet Genom* 2013; **23**: 34-37.

11 Takagi S, Baba S, Iwai N, Fukuda M, Katsuya T, Higaki J, Mannami T, Ogata J, Goto Y, Ogihara T. The aldehyde dehydrogenase 2 gene is a risk factor for hypertension in Japanese but does not alter the sensitivity to pressor effects of alcohol: the Suita study. *Hypertens Res* 2001; **24**: 365-370.

12 Saito K, Yokoyama T, Yoshiike N, Date C, Yamamoto A, Muramatsu M, Tanaka H. Do the ethanol metabolizing enzymes modify the relationship between alcohol consumption and blood pressure? *J Hypertens* 2003; **21**: 1097-1105.

13 Tsuritani I, Ikai E, Date T, Suzuki Y, Ishizaki M, Yamada Y. Polymorphism in ALDH2-genotype in Japanese men and the alcohol-blood pressure relationship. *Am J*

Hypertens 1995; **8**: 1053-1059.

14 Vasdev S, Sampson CA, Prabhakaran VM. Platelet-free calcium and vascular calcium uptake in ethanol-induced hypertensive rats. *Hypertension* 1991; **18**: 116-122.

15 Vasdev S, Gupta IP, Sampson CA, Longerich L, Parai S. Ethanol induced hypertension in rats: reversibility and role of intracellular cytosolic calcium. *Artery* 1993; **20**:19-43.

16 Vasdev S, Mian T, Longerich L, Prabhakaran V, Parai S. N-acetyl cysteine attenuates ethanol induced hypertension in rats. *Artery* 1995; **21**: 312-316.

17 Vasdev S, Wadhawan S, Ford CA, Parai S, Longerich L, Gadag V. Dietary vitamin B6 supplementation prevents ethanol-induced hypertension in rats. *Nutr Metab Cardiovasc Dis* 1999; **9**: 55-63.

18 Ministry of Health, Labour and Welfare, Japan. *The National Health and Nutrition Survey in Japan 2010*. Tokyo: Office for Life-style Related Diseases Control,

General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare, 2013 (in Japanese).

19 Ministry of Health, Labour and Welfare, Japan. The National Health and Nutrition Survey in Japan 2010. http://www.mhlw.go.jp/bunya/kenkou/ eiyou/dl/ h22-houkoku-03.pdf (in Japanese, 2015.11.02 access).

20 Yokoyama T, Yokoyama A, Kato H, Tsujinaka T, Muto M, Omori T, Haneda T, Kumagai Y, Igaki H, Yokoyama M, Watanabe H, Yoshimizu H. Alcohol flushing, alcohol and aldehyde dehydrogenase genotypes, and risk for esophageal squamous cell carcinoma in Japanese men. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 1227-1233.

21 Yokoyama A, Kato H, Yokoyama T, Igaki H, Tsujinaka T, Muto M, Omori T, Kumagai Y, Yokoyama M, Watanabe H. Esophageal squamous cell carcinoma and aldehyde dehydrogenase-2 genotypes in Japanese females. *Alcohol Clin Exp Res* 2006; **30**: 491-500.

22 James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Jr., Svetkey LP, Taler SJ, Townsend RR, Wright JT, Jr., Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507-520.

23 Ueshima H, Shimamoto T, Iida M, Konishi M, Tanigaki M, Doi M, Tsujioka K, Nagano E, Tsuda C, Ozawa H, Kojima S, Komachi Y. Alcohol intake and hypertension among urban and rural Japanese populations. *J Chronic Dis* 1984; **37**: 585-592.

24 Itoh T, Matsumoto M, Nakamura M, Okada A, Shirahashi N, Hougaku H, Hashimoto H, Sakaguchi M, Handa N, Takeshita T, Morimoto K, Hori M. Effects of daily alcohol intake on the blood pressure differ depending on an individual's sensitivity to alcohol: oriental flushing as a sign to stop drinking for health reasons. *J Hypertens* 1997; **15**: 1211-1217.

25 Jung JG, Kim JS, Yoon SJ, Oh MK. Relationships among alcohol consumption, facial

flushing response, and metabolic syndrome in healthy men. *Ann Epidemiol* 2012; **22**: 480-486.

26 Nishimura FT, Fukunaga T, Kajiura H, Umeno K, Takakura H, Ono T, Nishijo H. Effects of aldehyde dehydrogenase-2 genotype on cardiovascular and endocrine responses to alcohol in young Japanese subjects. *Auton Neurosci* 2002; **102**: 60-70.

27 Yamada Y, Sun F, Tsuritani I, Honda R. Genetic differences in ethanol metabolizing enzymes and blood pressure in Japanese alcohol consumers. *J Hum Hypertens* 2002; **16**: 479-486.

28 Okayama A, Ueshima H, Yamakawa M, Kita Y. Low-Km aldehyde dehydrogenase deficiency does not influence the elevation of blood pressure by alcohol. *J Hum Hypertens* 1994; **8**: 205-208.

29 Marmot MG, Elliott P, Shipley MJ, Dyer AR, Ueshima H, Beevers DG, Stamler R, Kesteloot H, Rose G, Stamler J. Alcohol and blood pressure: the INTERSALT study. *BMJ*

1994; **308**: 1263-1267.

30 Wakabayashi I. History of antihypertensive therapy influences the relationships of alcohol with blood pressure and pulse pressure in older men. *Am J Hypertens* 2010; **23**: 633-638.

31 Wagner A, Sadoun A, Dallongeville J, Ferrieres J, Amouyel P, Ruidavets JB, Arveiler D. High blood pressure prevalence and control in a middle-aged French population and their associated factors: the MONA LISA study. *J Hypertens* 2011; **29**: 43-50.

32 Goedde HW, Agarwal DP, Fritze G, Meier-Tackmann D, Singh S, Beckmann G, Bhatia K, Chen LZ, Fang B, Lisker R, Paik YK, Rothhammer F, Saha N, Segal B, Srivastava LM, Czeizel A. Distribution of ADH2 and ALDH2 genotypes in different populations. *Hum Genet* 1992; 88: 344-346.

33 Ohira T, Tanigawa T, Tabata M, Imano H, Kitamura A, Kiyama M, Sato S, Okamura T, Cui R, Koike K. A, Shimamoto T, Iso H. Effects of habitual alcohol intake

on ambulatory blood pressure, heart rate, and its variability among Japanese men.

Hypertension 2009; **53**: 13-19.

TABLE 1. Distribution of population by age and sex between NIPPON DATA2010 and Nutrition Survey of Japan in 2010 (NHNS2010)

Men			Women		
Age (years)	**NIPPON DATA2010 (%)**	**NHNS2010 (%)**	**Age (years)**	**NIPPON DATA2010 (%)**	**NHNS2010 (%)**
20-29	4.6	4.7	**20-29**	4.6	4.6
30-39	9.0	10.1	**30-39**	14	14.2
40-49	10.3	11.0	**40-49**	11.0	13.5
50-59	15.6	16.2	**50-59**	17.2	17.2
60-69	30.4	28.9	**60-69**	26.2	24.9
70≤	30.2	29.1	**70≤**	26.8	25.5
total (n)	1,239	1,598	**total (n)**	1,659	2,275

TABLE 2. Study participants' baseline characteristics according to the alcohol intake and flushing response, NIPPON DATA2010

Men (n = 1,139)

	Flusher				*P* for linear trend	Non-flusher				*P* for linear trend	*P* for interaction
	Alcohol intake					Alcohol intake					
	0 *gou* [a]/day	0 < *gou* /day < 1	1 ≤ *gou* /day < 2	2 ≤ *gou* /day		0 *gou* /day	0 < *gou* /day < 1	1 ≤ *gou* /day < 2	2 ≤ *gou* /day		
Number	210	219	103	51		58	222	176	100		
Age (year) (mean ± SD)	60.5 ± 17.1	60.7 ± 15.6	61.3 ± 11.8	59.6 ± 13.2	0.971	52.3 ± 19.8	58.9 ± 16.8	60.3 ± 14.3	56.4 ± 14.0	0.303	0.427
SBP (mmHg) (mean ± SD)	132.6 ± 16.7	135.1 ± 17.2	141.0 ± 18.4	139.1 ± 18.2	<0.001	131.7 ± 17.3	134.3 ± 18.8	138.8 ± 15.6	140.8 ± 18.1	<0.001	0.775
DBP (mmHg) (mean ± SD)	79.0 ± 9.7	81.2 ± 10.1	85.8 ± 11.5	86.3 ± 10.5	<0.001	79.2 ± 10.7	81.9 ± 9.9	83.9 ± 11.1	85.3 ± 11.5	<0.001	0.202
BMI ≥25 kg/m^2 (number, %)	32.4	27.9	39.8	29.4	0.665	43.1	34.7	35.8	36.0	0.627	0.516
Smoking status (number, %)											
Current-smoker	30.5	28.8	35.9	37.3	0.234	19.0	21.2	29.6	37.0	0.001	0.090
Ex-smoker	37.6	43.8	48.5	51.0	0.026	31.0	45.1	44.9	41.0	0.513	0.296
Never-smoker	31.9	27.4	15.5	11.8	<0.001	50.0	33.8	25.6	22.0	<0.001	0.925
Use of antihypertensive drugs (number, %)											
Yes	26.2	31.1	32.0	27.5	0.471	29.3	33.3	38.1	27.0	0.857	0.529
Present illness of diabetes mellitus (number, %)											
Yes	16.2	16.0	18.5	21.6	0.358	8.6	21.2	17.6	18.0	0.606	0.799
Present illness of dyslipidemia (number, %)											
Yes	36.7	38.4	37.9	25.5	0.353	25.9	39.6	36.4	31.0	0.826	0.635

Women (n = 1,263)

	Flusher			*P* for linear trend	Non-flusher			*P* for linear trend	*P* for interaction
	Alcohol intake				Alcohol intake				
	0 *gou* [a]/day	0 < *gou* /day < 1	1 ≤ *gou* /day		0 *gou* /day	0 < *gou* /day < 1	1 ≤ *gou* /day		
Number	397	185	15		280	316	70		
Age (year) (mean ± SD)	54.9 ± 15.4	54.3 ± 15.3	50.9 ± 12.1	0.397	59.3 ± 16.6	52.4 ± 16.1	50.6 ± 13.4	<0.001	0.005
SBP (mmHg) (mean ± SD)	126.6 ± 18.7	126.9 ± 19.7	123.4 ± 14.7	0.875	131.4 ± 20.5	124.9 ± 18.7	125.2 ± 16.0	<0.001	0.029
DBP (mmHg) (mean ± SD)	76.2 ± 10.2	77.4 ± 11.7	74.6 ± 8.6	0.467	77.1 ± 11.1	77.0 ± 10.6	77.0 ± 9.5	0.887	0.508
BMI ≥25 kg/m^2 (number, %)	22.7	22.2	6.7	0.399	22.9	20.6	15.7	0.198	0.902
Smoking status (number, %)									
Current-smoker	9.6	5.4	20.0	0.514	5.0	8.9	21.4	<0.001	0.005
Ex-smoker	7.8	12.4	26.7	0.009	6.8	10.8	22.9	<0.001	0.811
Never-smoker	82.6	82.2	53.3	0.123	88.2	80.4	55.7	<0.001	0.023
Use of antihypertensive drugs (number, %)									
Yes	15.9	20.5	20.0	0.184	30.0	18.4	8.6	<0.001	<0.001
Present illness of diabetes mellitus (number, %)									
Yes	8.3	8.1	6.7	0.856	9.6	5.7	4.3	0.044	0.233
Present illness of dyslipidemia (number, %)									
Yes	37.3	38.4	26.7	0.835	37.5	32.6	17.1	0.003	0.087

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index

[a] *Gou* : A traditional Japanese unit of volume. One *gou* is equivalent to 22.1 g of ethanol.

TABLE 3. Relation between alcohol intake and hypertension according to flushing response

Men (n = 1,139)

	OR (95%CI)					
	Alcohol intake (gou/day)				*P* for linear trend	*P* for interaction
	0 *gou* [a]/day	0 < *gou* /day < 1	1 ≤ *gou* /day < 2	2 ≤ *gou* /day		
Flusher (n = 583)						
Number of subjects with hypertension (%)	110/210 (52.4)	116/219 (53.0)	69/103 (67.0)	31/51 (60.8)		
Alcohol intake (median, *g* /week)	0.0	38.7	232.1	386.8		
Crude OR (95% CI)	1.00 (Reference.)	1.02 (0.70-1.50)	1.85 (1.13-3.02)*	1.41 (0.76-2.63)		
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	1.10 (0.71-1.72)	1.86 (1.07-3.23)*	1.91 (0.92-3.96)	0.016	
Non flusher (n = 556)						0.360
Number of subjects with hypertension (%)	24/58 (41.4)	123/222 (55.4)	121/176 (68.8)	65/100 (65.0)		
Alcohol intake (median, *g* /week)	0.0	52.5	232.1	386.8		
Crude OR (95% CI)	1.00 (Reference.)	1.76 (0.98-3.16)	3.12 (1.69-5.75)*	2.63 (1.35-5.11)*		
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	1.28 (0.62-2.68)	2.43 (1.14-5.17)*	2.62 (1.16-5.92)*	0.001	

Women (n = 1,263)

	OR (95%CI)				
	Alcohol intake (gou/day)				
	0 *gou* [a]/day	0 < *gou* /day < 1	1 ≤ *gou* /day	*P* for linear trend	*P* for interaction
Flusher (n = 597)					
Number of subjects with hypertension (%)	136/397 (34.3)	71/185 (38.4)	5/15 (33.3)		
Alcohol intake (median, *g* /week)	0.0	16.6	232.1		
Crude OR (95% CI)	1.00 (Reference.)	1.20 (0.83-1.72)	0.96 (0.32-2.86)		
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	1.34 (0.86-2.08)	2.31 (0.64-8.40)	0.093	
					0.052
Non flusher (n = 666)					
Number of subjects with hypertension (%)	134/280 (47.9)	96/316 (30.4)	21/70 (30.0)		
Alcohol intake (median, *g* /week)	0.0	27.6	232.1		
Crude OR (95% CI)	1.00 (Reference.)	0.48 (0.34-0.67)*	0.47 (0.27-0.82)*		
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	0.66 (0.43-1.01)	0.99 (0.48-2.04)	0.315	

Abbreviations: OR, odds ratio; 95% CI , 95% confidence interval

[a] *Gou* : A traditional Japanese unit of volume. One gou is equivalent to 22.1 g of ethanol.

[b] Adjusted for age (continuous variable), BMI (<18.5, 18.5-24.9, ≥25.0), smoking status (current, ex, never), present illness of diabetes mellitus (yes, no) and present illness of dyslipidemia (yes,no)

*$P < 0.05$

TABLE 4. Relation between alcohol intake and hypertension among participants who did not take antihypertensive drugs

Men (n = 784)

	OR (95%CI)					
	Alcohol intake (gou/day)				*P* for linear trend	*P* for interaction
	0 *gou*[a]/day	0 < *gou* /day < 1	1 ≤ *gou* /day < 2	2 ≤ *gou* /day		
Flusher (n = 413)						
Number of subjects with hypertension (%)	55/155 (35.5)	48/151 (31.8)	36/70 (51.4)	17/37 (45.9)		
SBP (mmHg); mean (95% CI)[b]	129.9 (126.3-133.5)	131.8 (128.0-135.5)	135.8 (131.0-140.5)	136.2 (130.4-142.1)	0.004	0.567
DBP (mmHg); mean (95% CI)[b]	78.5 (76.3-80.7)	80.4 (78.1-82.6)	84.3 (81.3-87.2)	85.3 (81.7-88.9)	<0.001	
Crude OR (95% CI)	1.00 (Reference.)	0.85 (0.53-1.36)	1.93 (1.09-3.41)*	1.55 (0.75-3.19)		
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	0.89 (0.53-1.49)	1.79 (0.97-3.34)	1.88 (0.84-4.23)	0.038	
						0.375
Non flusher (n = 371)						
Number of subjects with hypertension (%)	7/41 (17.1)	49/148 (33.1)	54/109 (49.5)	38/73 (52.1)		
SBP (mmHg); mean (95% CI)[b]	130.3 (123.7-137.0)	128.9 (124.2-133.6)	134.4 (129.0-139.8)	137.0 (131.4-142.6)	0.001	
DBP (mmHg); mean (95% CI)[b]	77.4 (73.0-81.8)	79.8 (76.6-82.9)	82.2 (78.6-85.8)	82.9 (79.1-86.6)	0.002	
Crude OR (95% CI)	1.00 (Reference.)	2.40 (0.995-5.81)	4.77 (1.95-11.68)*	5.27 (2.07-13.42)*		0.136
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	2.03 (0.78-5.31)	4.00 (1.51-10.57)*	4.66 (1.69-12.81)*	<0.001	

Women (n = 1,011)

	OR (95%CI)				
	Alcohol intake (gou/day)				
	0 *gou*[a]/day	0 < *gou* /day < 1	1 ≤ *gou* /day	*P* for linear trend	*P* for interaction
Flusher (n = 493)					
Number of subjects with hypertension (%)	73/334 (21.9)	33/147 (22.4)	2/12 (16.7)		
SBP (mmHg); mean (95% CI)[b]	124.5 (120.9-128.1)	124.4 (115.5-133.8)	124.6 (115.5-133.8)	0.967	0.859
DBP (mmHg); mean (95% CI)[b]	75.2 (73.0-77.5)	76.0 (73.5-78.6)	74.4 (68.6-80.2)	0.583	
Crude OR (95% CI)	1.00 (Reference.)	1.04 (0.65-1.65)	0.72 (0.15-3.34)		
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	1.13 (0.68-1.90)	1.25 (0.22-7.01)	0.607	
					0.865
Non flusher (n = 518)					
Number of subjects with hypertension (%)	50/196 (25.5)	38/258 (14.7)	15/64 (23.4)		
SBP (mmHg); mean (95% CI)[b]	122.6 (118.5-126.8)	120.9 (116.9-125.0)	123.6 (118.6-128.6)	0.860	
DBP (mmHg); mean (95% CI)[b]	74.1 (71.4-76.8)	74.5 (71.9-77.1)	75.7 (72.5-78.9)	0.288	
Crude OR (95% CI)	1.00 (Reference.)	0.50 (0.32-0.81)*	0.89 (0.46-1.73)		0.522
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	0.60 (0.35-1.03)	1.28 (0.58-2.82)	0.711	

Abbreviations: OR, odds ratio; 95% CI , 95% confidence interval

[a] *Gou* : A traditional Japanese unit of volume. One gou is equivalent to 22.1 g of ethanol.

[b] Adjusted for age (continuous variable), BMI (<18.5, 18.5-24.9, ≥25.0), smoking status (current, ex, never), present illness of diabetes mellitus (yes, no) and present illness of dyslipidemia (yes,no)

*$P < 0.05$

TABLE 5. Relation between alcohol intake and uncontrolled hypertension among participants who took antihypertensive drugs

Men (n = 355)

	OR (95%CI)					
	Alcohol intake (gou/day)				*P* for linear trend	*P* for interaction
	0 *gou*[a]/day	0 < *gou* /day < 1	1 ≤ *gou* /day < 2	2 ≤ *gou* /day		
Flusher (n = 170)						
Number of uncontrolled hypertension (BP = 140/90) (%)	23/55 (41.8)	41/68 (60.3)	23/33 (69.7)	10/14 (71.4)		
SBP (mmHg); mean (95% CI)[b]	136.3 (131.9-140.7)	141.1 (137.1-145.0)	146.2 (140.8-151.7)	144.7 (136.6-152.8)	0.004	0.334
DBP (mmHg); mean (95% CI)[b]	78.5 (75.4-81.5)	81.7 (78.9-84.5)	84.4 (80.5-88.2)	87.0 (81.3-92.7)	0.001	
Crude OR (95% CI)	1.00 (Reference.)	2.11 (1.03-4.35)*	3.20 (1.28-7.99)*	3.48 (0.97-12.47)		
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	2.20 (1.04-4.68)*	3.30 (1.26-8.63)*	3.78 (1.02-14.06)*	0.007	0.168
Non flusher (n = 185)						
Number of uncontrolled hypertension (BP = 140/90) (%)	10/17 (58.8)	45/74 (60.8)	49/67 (73.1)	20/27 (74.1)		
SBP (mmHg); mean (95% CI)[b]	143.3 (135.5-151.2)	145.6 (141.9-149.4)	145.0 (141.0-149.0)	150.8 (144.6-156.9)	0.188	
DBP (mmHg); mean (95% CI)[b]	79.2 (74.2-84.1)	83.0 (80.6-85.4)	82.2 (79.7-84.7)	84.1 (80.3-88.0)	0.286	
Crude OR (95% CI)	1.00 (Reference.)	1.09 (0.37-3.18)	1.91 (0.63-5.76)	2.00 (0.55-7.29)		0.481
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	1.19 (0.39-3.67)	2.02 (0.64-6.33)	2.03 (0.53-7.73)	0.114	

Women (n = 252)

	OR (95%CI)				
	Alcohol intake (gou/day)				
	0 *gou*[a]/day	0 < *gou* /day < 1	1 ≤ *gou* /day	*P* for linear trend	*P* for interaction
Flusher (n = 104)					
Number of uncontrolled hypertension (BP = 140/90) (%)	35/63 (55.6)	22/38 (57.9)	2/3 (66.7)		
SBP (mmHg); mean (95% CI)[b]	143.2 (135.2-151.2)	144.7 (136.3-153.1)	138.0 (119.5-156.5)	0.881	0.451
DBP (mmHg); mean (95% CI)[b]	74.5 (69.2-79.7)	77.8 (72.3-83.2)	76.9 (64.9-89.0)	0.130	
Crude OR (95% CI)	1.00 (Reference.)	1.10 (0.49-2.48)	1.60 (0.14-18.57)		
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	1.18 (0.50-2.83)	1.43 (0.10-19.98)	0.664	0.874
Non flusher (n= 148)					
Number of uncontrolled hypertension (BP = 140/90) (%)	49/84 (58.3)	31/58 (53.4)	3/6 (50.0)		
SBP (mmHg); mean (95%CI)[b]	143.3 (135.9-150.7)	142.3 (135.4-149.2)	146.5 (133.6-159.4)	0.963	
DBP (mmHg); mean (95%CI)[b]	77.2 (72.0-82.4)	80.2 (75.4-85.1)	79.3 (70.1-88.4)	0.162	
Crude OR (95% CI)	1.00 (Reference.)	0.82 (0.42-1.61)	0.71 (0.14-3.75)		0.410
Multiple adjusted OR (95% CI)[b]	1.00 (Reference.)	0.98 (0.46-2.09)	1.05 (0.14-7.99)	0.991	

Abbreviations: OR, odds ratio; 95% CI , 95% confidence interval

[a] *Gou* : A traditional Japanese unit of volume. One gou is equivalent to 22.1 g of ethanol.

[b] Adjusted for age (continuous variable), BMI (<18.5, 18.5-24.9, ≥25.0), smoking status (current, ex, never), present illness of diabetes mellitus (yes, no) and present illness of dyslipidemia (yes,no)

*$P < 0.05$