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1 Title page

2 Relation between Alcohol Consumption and Arterial Stiffness: a Cross-sectional Study of
3 Middle-aged Japanese Women and Men

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5 S. Sasaki ^{1,2}; E. Yoshioka, MD, PhD³; Y. Saijo, MD, PhD³; T. Kita, PhD⁴; E. Okada, PhD¹; A.

6 Tamakoshi, MD, PhD¹; R. Kishi, MD, MPH, PhD⁵

7

8 ¹Department of Public Health Sciences, Hokkaido University Graduate School of Medicine, Kita 15,
9 Nishi 7, Kita-ku, Sapporo, 060-8638, Japan

10 ²Department of Physical Therapy, Faculty of Human Science, Hokkaido Bunkyo University, 5-196-1
11 Kogane-chuo, Eniwa, 061-1449, Japan

12 ³Department of Health Science, Asahikawa Medical University, Midorigaoka E2-1-1-1, Asahikawa,
13 078-8510, Japan

14 ⁴Department of Medical Management and Informatics, Hokkaido Information University,
15 Nishi-Nopporo 59-2, Ebetsu, 069-8585, Japan

16 ⁵Center for Environmental and Health Sciences, Hokkaido University, Kita 12, Nishi 7, Kita-ku,
17 Sapporo, 060-0812, Japan

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1 **Corresponding author**

2 R. Kishi, MD, MPH, PhD, Center for Environmental and Health Sciences, Hokkaido University, Kita

3 12, Nishi 7, Kita-ku, Sapporo, 060-0812, Japan

4 Tel.: 81-11-706-4747; Fax: 81- 11-706-4725; E-mail: rkishi@med.hokudai.ac.jp

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Abstract

Epidemiological data indicate the existence of a J-shaped association between alcohol consumption and cardiovascular morbidity and mortality. However, studies assessing the relationship between alcohol consumption and pulse wave velocity (PWV) as a marker of arterial stiffness have provided inconsistent results. In addition, data regarding the effect of alcohol on arterial stiffness in women has been limited. This study aimed to clarify the relationship between alcohol consumption and PWV among female and male workers in Japan. Study participants were local government employees in Hokkaido, Japan, who underwent annual health check-ups. All data were collected using self-administered questionnaires. The average daily alcohol consumption of the previous month, based on the alcohol concentration of each beverage type (g/day, ethanol equivalent), was estimated according to the frequency and amount of consumption. Data from 3893 participants (812 women and 3081 men) were analyzed. Compared with subjects who consumed <10 g/day, non-drinkers had significantly higher PWV in women. In men, compared with those who reportedly drank 20–39 g/day, non-drinkers and those who drank <20 g/day and ≥ 60 g/day had significantly higher PWV. Alcohol consumption showed a J-shaped association with PWV in men (P for quadratic term <0.036) and marginally in women (P <0.056). The results of stratified analyses by age groups showed a significant J-shaped association which was most notable for men ≥ 45 years (P <0.005). In middle-aged Japanese women and men, light-to-moderate alcohol consumption is associated with lower PWV, which in turn

1 correlates with a reduction in vascular stiffness.

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3 **Key Words:**

4 Alcohol consumption

5 Arterial stiffness

6 Brachial-ankle pulse wave velocity

7 Cardiovascular disease

8 Cardiovascular protection

9 Epidemiology

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11 **Non-standard Abbreviations and Acronyms:**

12 **PWV**, pulse wave velocity

13 **baPWV**, brachial-ankle pulse wave velocity

14 **TC**, total cholesterol

15 **TG**, triglyceride

16 **ABI**, ankle-brachial index

17 **BMI**, body mass index

18 **HDL-C**, high-density lipoprotein cholesterol

1 **LDL-C**, low-density lipoprotein cholesterol

2 **SBP**, systolic blood pressure

3 **DBP**, diastolic blood pressure

4 **HR**, heart rate

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1 **Introduction**

2 A large number of epidemiological studies have reported that light-to-moderate alcohol
3 consumption reduces the risk of cardiovascular disease, whereas excessive alcohol consumption
4 increases the risk in men and women in Western countries and Asia.[1-4] Mechanisms by which
5 excessive alcohol consumption leads to increased cardiovascular risk have been linked to increased
6 blood pressure, inhibition of platelet aggregation, and activation of the fibrinolytic system.[5, 6] The
7 cardiovascular benefit of light-to-moderate alcohol consumption has been explained by its positive
8 effect on lipid metabolism, platelet function, inflammatory processes, and endothelial function.[5-9]
9 Therefore, alcohol has both beneficial and adverse effects on arteriosclerosis depending on the amount
10 consumed.

11 Pulse wave velocity (PWV) is known to be an early indicator of arterial stiffness, and its elevation is
12 associated with the development of arteriosclerotic diseases.[10-12] The results of previous studies of
13 the effect of alcohol consumption on PWV in men were inconsistent. A U-shaped association was
14 reported in one study,[13] whereas no or positive association was observed in other studies.[14, 15]
15 Moreover, studies investigating the relationship between alcohol consumption and PWV in women
16 are limited. Although two previous studies in Dutch postmenopausal women and young women
17 reported an inverse relationship between alcohol and PWV, [16, 17] the effects of alcohol on PWV,
18 based on the amount of alcohol consumed, have not been evaluated.

1 In this study, we focused on the importance of the amount of alcohol while investigating the
2 relationship between early cardiovascular markers, such as PWV an index of arterial stiffness, and
3 alcohol consumption in Japanese middle-aged women and men.

Methods

Study Population

Participants were local government employees (2194 women and 8229 men, age: 35–62 years) in Sapporo City who underwent an annual health check-up between April 2003 and March 2004. Data were collected using a self-administered questionnaire, which included items related to alcohol consumption, clinical history, family history, smoking, exercise frequency, and educational background. The questionnaire was distributed to subjects before their annual health check-up and collected during the check-up. Completed questionnaires and written informed consent to review the data were obtained from 1051 women and 3962 men (response rate: women 47.9%, men 48.2%). A total of 1120 subjects were excluded for the following reasons: PWV not measured ($n = 613$), missing data for alcohol consumption and blood pressure ($n = 22$), low ankle–brachial pressure index [ABI, <0.9 ; $n = 10$; brachial–ankle (ba) PWV values in subjects with peripheral artery disease could not be accurately evaluated], subjects taking medication for hypertension ($n = 354$), or a history of coronary disease or stroke ($n = 121$). The final study group thus comprised 812 women and 3081 men.

This study was conducted with the written informed consent of all subjects and was approved by the institutional ethical board for epidemiological studies of Hokkaido University Graduate School of Medicine.

Assessment of alcohol consumption

Alcohol consumption was assessed using a self-administered questionnaire covering the previous month. Each subject was asked about average drinking frequency (days/week) and average amount of different types of alcoholic beverages consumed each time, including beer, sake (rice wine), shochu (traditional Japanese distilled spirit), whisky, wine, or other mixed drinks. The average daily alcohol consumption (g/day, ethanol equivalent) was calculated according to the frequency and amount of alcohol consumed using the following alcohol concentrations of each beverage type: 5% for beer, 15% for sake, 25% for shochu, 40% for whisky, 12% for wine, and 5% for other mixed drinks.[18]

The subjects were divided into the following five categories by sex: non-drinkers, <10 g/day, 10–19 g/day, 20–29 g/day, and ≥ 30 g/day for women and non-drinkers, <20 g/day, 20–39 g/day, 40–59 g/day, and ≥ 60 g/day for men. Categorical values were selected on the basis of the generally accepted guideline that alcohol consumption should be limited to no more than 10–20 g/day for women and no more than 20–30 g/day for men in order to prevent hypertension.[19]

PWV Measurements

A volume-plethysmographic device was used to measure baPWV (Form PWV/AVI; model BP-203RPE II, Colin Co., Komaki, Japan).[12] This device records a phonocardiogram, electrocardiogram, and volume pulse form and arterial blood pressure at the left and right brachial and

bilateral ankles. A time-phase analysis between right brachial and volume waveforms at both ankles was used for calculating baPWV. The characteristic points of waveforms were determined automatically, and the validity of baPWV measurements has been reported previously.[20] Blood pressure, heart rate (HR), and ABI were measured using a pulse-wave velocimeter concurrently with PWV measurement. ABI is the ratio of ankle systolic blood pressure (SBP) to brachial SBP. Right and left ABIs were measured simultaneously. In all studies, baPWV was obtained after at least 5 min of rest.

Covariates

Anthropometric measurements (height, body weight) at health check-ups were assessed using a standardized protocol. Body mass index (BMI) was calculated as $\text{weight (kg)}/\text{height (m)}^2$. Blood samples were drawn from the antecubital vein of seated subjects with minimal tourniquet use after a 12-h fast. Specimens were collected in siliconized glass vacuum tubes containing sodium fluoride for blood glucose. Total cholesterol (TC) levels were measured by an enzymatic method (Wako, Osaka, Japan), triglyceride (TG) levels by an enzymatic method (Daiichi Pure Chemicals, Tokyo, Japan), high-density lipoprotein cholesterol (HDL-C) levels by a direct method (Daiichi Pure Chemicals), and blood glucose by an amperometric method (Arkray, Kyoto, Japan).

Educational background was categorized as either “high school education or less” or “more than

high school.” Frequency of leisure time exercise (with perspiration) was categorized as “rarely or never,” “1–2 times/week,” or “3 times/week or more.” Smoking status was categorized as “non-smoker” (never smoked), “ex-smoker,” or “current smoker. We asked about current use of hormone (estrogen) replacement therapy in the questionnaire.

Statistical Analyses

All analyses were performed for women and men separately. Data are presented as mean $\pm$ standard deviation, median (interquartile range) for variables with a skewed distribution, or percentages. TG values were log-transformed to achieve an approximately normal distribution. Differences in the distribution of variables according to alcohol consumption were tested for statistical significance using one-way ANOVA for continuous variables or the chi-square test for categorical variables. For regression analysis, we selected reference categories of alcohol consumption (<10 g/day for women and 20–39 g/day for men) for the following reasons: some Japanese cohort studies reported that <46g/day of alcohol consumption reduced mortality from cardiovascular disease and incidence coronary heart disease in men.[3, 21] With regard to women, a previous study showed that women experience higher cardiovascular risk when men and women consume the same amount of alcohol because the genders metabolize ethanol differently.[22] Therefore, we decided to use a lower reference category for women than for men. Subsequently, we performed multiple liner regression

analysis to investigate the association between alcohol consumption and mean baPWV using the following three models: 1 = adjusted for age, SBP, and HR; 2 = adjusted for model 1 variables plus menopausal status (for women), medication for diabetes, medication for hyperlipemia, BMI, TC, TG, HDL-C, and fasting blood sugar (FBS); and 3 = adjusted for model 2 plus lifestyle factors (educational background, frequency of exercise, and smoking status). In addition, to investigate the non-linear relationship between alcohol consumption and baPWV, the estimated quantitative median value for each category of alcohol consumption was included as linear and quadratic terms in the model. Finally, to clarify the effect of age on the relation between alcohol and baPWV, we performed stratified analyses by age group in men only, because the sample size was too small to analyze in women. All analyses were conducted using JMP Pro software, version 10.0.0 for windows (SAS Institute, Cary, NC, USA), and statistical significance was defined as a two-tailed *P* value of <0.05.

Results

A large number of women (46.7%) reported no consumption of alcohol compared with men (27.7%). Characteristics of women participants stratified by the category of alcohol consumption are reported in Table 1. The mean PWV value was the lowest in the subjects belonging to the <10 g/day alcohol consumption category compared with non-drinkers and subjects belonging to the heavier categories of alcohol consumption, and was elevated with an increase in the amount of alcohol consumed. SBP and diastolic blood pressure (DBP), HDL-C, and uric acid showed a positive linear trend related to alcohol consumption, whereas low-density lipoprotein cholesterol (LDL-C) showed an inverse linear trend. Table 2 shows the characteristics of male participants based on the alcohol consumption category. The mean PWV value, age, and TG levels were the lowest in subjects belonging to the <20 g/day alcohol consumption category compared with non-drinkers and subjects belonging to the heavier categories of alcohol consumption. The mean PWV value increased with an increase in the amount of alcohol consumed. SBP, DBP, HDL-C, FBS, and uric acid showed a positive linear trend related to alcohol consumption, whereas LDL-C showed an inverse linear trend. The results of multiple linear regression analysis for alcohol consumption and PWV by sex, adjusted for potential confounders, are presented in Tables 3 and 4. In women, non-drinkers had significantly elevated PWV compared with subjects consuming <10 g/day of alcohol. In men, compared with those who consumed 20–39 g/day of alcohol, non-drinkers and those who consumed <20 g/day and ≥ 60

g/day of alcohol had significantly elevated PWV. There was no change in this finding after adjustment for the hormone replacement therapy included in the final models. In the present study, postmenopausal hormone replacement therapy did not affect the association between alcohol consumption and PWV. A J-shaped association between alcohol consumption and PWV was significant for men and marginally significant for women, after adjustment for various arteriosclerotic risk factors (P for quadratic term = 0.056 in women and 0.036 in men). We also examined effect modification by age group (<45 years and ≥ 45 years) for men (Table 5). A significant J-shaped association was found for men ≥ 45 years (P for quadratic term = 0.005), but not for the younger age group. (P for quadratic term = 0.938).

Discussion

The present study showed that in women, non-drinking was significantly associated with higher PWV compared with drinking of <10 g/day of alcohol. In men, non-drinkers and those who drank <20 g/day and ≥ 60 g/day had significantly higher PWV compared with those who drank 20–39 g/day. We examined whether the effects of alcohol consumption on PWV were linear or not, by testing a quadratic term in the model containing potential confounders. A J-shaped association between alcohol consumption and PWV was significant for men and marginally significant for women. In the analyses stratified by age group, the protective effect of light alcohol consumption was evident only for men ≥ 45 years.

To the best of our knowledge, there are a limited number of studies reporting the association between alcohol consumption and PWV in women. A cross-sectional study in Japanese–American women evaluating drinking history reported that the risk for high PWV was lower among current drinkers and ex-drinkers than among non-drinkers.[23] Two cross-sectional studies in Dutch women suggested that light-to-moderate alcohol consumption, evaluated on the basis of glass per day or week, is associated with lower PWV.[16, 17] The advantages of our study include large sample size and more detailed estimation of the average daily alcohol consumption. Our results demonstrated that women who consumed a low amount of alcohol (1–10 g/day) had lower PWV compared with non-drinkers. This association was not affected by controlling for potential confounders. However, a

J-shaped association between alcohol consumption and PWV was marginal in women. It may be that the numbers of women in our study, particularly in the group of 20-29g/day and 30g/day, were too small for statistical detection of a J-shaped association. Further research is needed to clarify the effect of alcohol consumption on arterial stiffness in women.

In men, a few studies investigating the effect of alcohol on PWV have reported conflicting results. A follow-up study in Japanese men suggested that alcohol consumption was not related to PWV.[14] Whereas a longitudinal study and a cross-sectional study in Japanese men reported that alcohol consumption was associated with increased PWV.[15, 24] Cross-sectional studies in Dutch middle-aged men and a follow-up study in Japanese men suggested the protective effects of light-to-moderate alcohol consumption on PWV.[13, 25] Consistent with these two studies, we found a J-shaped association between alcohol consumption and PWV. However, the sample size of the previous two studies was comparatively small, while that of ours was larger. Men who did not consume alcohol and those who consumed <20 g/day and ≥ 60 g/day of alcohol had significantly higher PWV compared with those who consumed 20–39 g/day of alcohol. We also examined effect modification by age among men; a J-shaped association was evident for men >45 years, but not for younger male adults. Consistent with the present study, a cross-sectional study reported that the protective effect of alcohol on PWV was not evident in young Dutch men. [17] They suggested that the beneficial effect obtained by moderate alcohol consumption in younger adults may be negligible

for lower risk of coronary heart disease. The association between alcohol consumption and PWV, as a marker of early stage atherosclerosis, might be influenced by age.

With regard to both women and men, our results indicated that light-to-moderate alcohol consumption among healthy Japanese workers was associated with reduced PWV, a marker of arterial stiffness. It would represent a plausible explanation for the beneficial health effect of alcohol. Some Japanese cohort studies reported that light to moderate alcohol consumption, <23g/day for women and <46g/day for men, was associated with a reduced risk of cardiovascular disease. [3, 21]

The mechanisms underlying the association between alcohol consumption and arterial stiffness are not completely understood. The protective effect on arteriosclerosis induced by light-to-moderate alcohol consumption may involve increasing HDL-C and improving lipid metabolic pathways.[6, 26]

In this study, the association between alcohol consumption and PWV remained after adjustments for serum lipid levels. The hypothesized beneficial relationship between alcohol consumption and arterial stiffness might also be associated with a decrease in inflammatory mediators such as interleukin-6, C-reactive protein, and tumor necrosis factor-alpha, improving insulin sensitivity and insulin resistance, and improving various metabolic pathways, such as vascular endothelial cell nitric oxide production.[6, 7, 27, 28] In contrast, excess alcohol consumption may elevate blood pressure,[6] an important determinant of arterial stiffness, through several mechanisms, such as influencing the vascular smooth muscle or stimulating the sympathetic nervous system or the

renin–angiotensin–aldosterone system.[29] Therefore, the effects of alcohol consumption on arterial stiffness have a dual contribution to the J-shaped association. These diverse mechanisms should be considered when evaluating the protective and adverse effect of alcohol on arterial stiffness.

Several limitations should be considered when interpreting our results. First, because our study had a cross-sectional design, the causal nature of the association between alcohol consumption and PWV cannot be determined. Second, because the response rate of our study was rather low (women 47.9%, men 48.2%), our subjects might not necessarily be representative of the general group of civil servants in Japan. However, because the average amount of alcohol consumed in our study did not differ from that by the general Japanese population,[30] we believe that our results were minimally affected by the population segment evaluated. Third, we relied on self-reported alcohol consumption in the present study, which could be susceptible to misclassification, particularly by those belonging to the heavier drinking category.[31] However, since we observed a positive correlation between alcohol consumption and HDL-C, selective underestimation of heavy drinkers seems unlikely. Fourth, although we focused on the importance of the amount of alcohol consumed, information on drinking patterns may be equally important. However, the percentage of heavy drinkers who reported consumption of a large amount of alcohol at one time was less than 2% for both women and men. Thus, it appears that binge drinking rarely occurred among our subjects. Fifth, we also considered the possibility of confounding dietary factors, which have not been measured in detail. Japanese

population consume large amount of fish and salt. However, the magnitude of association between alcohol consumption and PWV was not influenced, even when adjusted for brief information about frequency intake of fish and salt. Sixth, as mentioned before, physical characteristics influence PWV measurements, and in a previous study an inverse relationship between body height and carotid-femoral PWV was reported. [32] While, the instrument that we used calculates the distance between sampling points of baPWV according to the height of the subject automatically. [20] In previous baPWV studies, the value was usually adjusted not for height but for BMI. Therefore, we showed BMI adjusted baPWV. Finally, because of the small sample size in women, it is possible that the J-shaped association between alcohol consumption and arterial stiffness was not detected.

Conclusion

The results of our study indicate that light-to-moderate alcohol consumption may be associated with reduced PWV as a marker of arterial stiffness in middle-aged Japanese women and men. Since the effect of alcohol consumption on arterial stiffness may contribute to a reduction in the incidence of cardiovascular disease, further research is needed to examine the most appropriate amount of alcohol, which could be suggested as a modifiable lifestyle factor.

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Disclosures

The authors declare no conflict of interest.

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References

1. Malyutina, S., Bobak, M., Kurilovitch, S., Gafarov, V., Simonova, G., Nikitin, Y., and Marmot, M. (2002). Relation between heavy and binge drinking and all-cause and cardiovascular mortality in Novosibirsk, Russia: a prospective cohort study. *Lancet* *360*, 1448-1454.
2. O'Keefe, J.H., Bybee, K.A., and Lavie, C.J. (2007). Alcohol and cardiovascular health: the razor-sharp double-edged sword. *J Am Coll Cardiol* *50*, 1009-1014.
3. Ikehara, S., Iso, H., Toyoshima, H., Date, C., Yamamoto, A., Kikuchi, S., Kondo, T., Watanabe, Y., Koizumi, A., Wada, Y., et al. (2008). Alcohol consumption and mortality from stroke and coronary heart disease among Japanese men and women: the Japan collaborative cohort study. *Stroke* *39*, 2936-2942.
4. Gaziano, J.M., Gaziano, T.A., Glynn, R.J., Sesso, H.D., Ajani, U.A., Stampfer, M.J., Manson, J.E., Hennekens, C.H., and Buring, J.E. (2000). Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort. *J Am Coll Cardiol* *35*, 96-105.
5. Imhof, A., Woodward, M., Doering, A., Helbecque, N., Loewel, H., Amouyel, P., Lowe, G.D., and Koenig, W. (2004). Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Augsburg, Glasgow, Lille). *Eur Heart J* *25*, 2092-2100.
6. Lucas, D.L., Brown, R.A., Wassef, M., and Giles, T.D. (2005). Alcohol and the cardiovascular system: research challenges and opportunities. *J Am Coll Cardiol* *45*, 1916-1924.
7. Bau, P.F., Bau, C.H., Rosito, G.A., Manfro, W.C., and Fuchs, F.D. (2007). Alcohol consumption, cardiovascular health, and endothelial function markers. *Alcohol* *41*, 479-488.
8. Whelan, A.P., Sutherland, W.H., McCormick, M.P., Yeoman, D.J., de Jong, S.A., and Williams, M.J. (2004). Effects of white and red wine on endothelial function in subjects with coronary artery disease. *Intern Med J* *34*, 224-228.
9. Rubin, R. (1999). Effect of ethanol on platelet function. *Alcohol Clin Exp Res* *23*, 1114-1118.
10. Vlachopoulos, C., Aznaouridis, K., and Stefanadis, C. (2010). Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* *55*, 1318-1327.
11. O'Rourke, M.F., and Hashimoto, J. (2007). Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* *50*, 1-13.
12. Yamashina, A., Tomiyama, H., Takeda, K., Tsuda, H., Arai, T., Hirose, K., Koji, Y., Hori, S.,

- and Yamamoto, Y. (2002). Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 25, 359-364.
13. Matsumoto, C., Tomiyama, H., Yamada, J., Yoshida, M., Shiina, K., Nagata, M., and Yamashina, A. (2009). Association of blood pressure levels with the effects of alcohol intake on the vasculature in Japanese men. *Hypertens Res* 32, 127-132.
14. Nakanishi, N., Suzuki, K., Kawashimo, H., Nakamura, K., and Tatara, K. (1998). Risk factors for the incidence of aortic stiffness by serial aortic pulse wave velocity measurement in middle-aged Japanese men. *Environ Health Prev Med* 3, 168-174.
15. Nakanishi, N., Kawashimo, H., Nakamura, K., Suzuki, K., Yoshida, H., Uzura, S., and Tatara, K. (2001). Association of alcohol consumption with increase in aortic stiffness: a 9-year longitudinal study in middle-aged Japanese men. *Ind Health* 39, 24-28.
16. Sierksma, A., Lebrun, C.E., van der Schouw, Y.T., Grobbee, D.E., Lamberts, S.W., Hendriks, H.F., and Bots, M.L. (2004). Alcohol consumption in relation to aortic stiffness and aortic wave reflections: a cross-sectional study in healthy postmenopausal women. *Arterioscler Thromb Vasc Biol* 24, 342-348.
17. van den Elzen, A.P., Sierksma, A., Oren, A., Vos, L.E., Witteman, J.C., Grobbee, D.E., Hendriks, H.F., Uiterwaal, C.S., and Bots, M.L. (2005). Alcohol intake and aortic stiffness in young men and women. *J Hypertens* 23, 731-735.
18. Higuchi, S. (2003). Alcohol health guidance manual for the promotion of Healthy Japan 21. In: Higuchi S, eds. (Tokyo: Institute of Social Insurance), pp. 102-110.
19. Mancia, G., De Backer, G., Dominiczak, A., Cifkova, R., Fagard, R., Germano, G., Grassi, G., Heagerty, A.M., Kjeldsen, S.E., Laurent, S., et al. (2007). 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 25, 1105-1187.
20. Yamashina, A., Tomiyama, H., Takeda, K., Tsuda, H., Arai, T., Hirose, K., Koji, Y., Hori, S., and Yamamoto, Y. (2002). Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 25, 359-364.
21. Kitamura, A., Iso, H., Sankai, T., Naito, Y., Sato, S., Kiyama, M., Okamura, T., Nakagawa, Y., Iida, M., Shimamoto, T., et al. (1998). Alcohol intake and premature coronary heart disease in urban Japanese men. *Am J Epidemiol* 147, 59-65.
22. Di Castelnuovo, A., Costanzo, S., Bagnardi, V., Donati, M.B., Iacoviello, L., and de Gaetano, G. (2006). Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med* 166, 2437-2445.
23. Namekata, T., Moore, D., Suzuki, K., Mori, M., Hatano, S., Hayashi, C., Abe, N., and Hasegawa, M. (1997). [A study of the association between the aortic pulse wave velocity

- 1 and atherosclerotic risk factors among Japanese Americans in Seattle, U.S.A]. *Nihon*
- 2 *Koshu Eisei Zasshi* 44, 942-951.
- 3 24. Kurihara, T., Tomiyama, H., Hashimoto, H., Yamamoto, Y., Yano, E., and Yamashina, A.
- 4 (2004). Excessive alcohol intake increases the risk of arterial stiffening in men with
- 5 normal blood pressure. *Hypertens Res* 27, 669-673.
- 6 25. Sierksma, A., Muller, M., van der Schouw, Y.T., Grobbee, D.E., Hendriks, H.F., and Bots,
- 7 M.L. (2004). Alcohol consumption and arterial stiffness in men. *J Hypertens* 22, 357-362.
- 8 26. Hannuksela, M.L., Liisanantti, M.K., and Savolainen, M.J. (2002). Effect of alcohol on
- 9 lipids and lipoproteins in relation to atherosclerosis. *Crit Rev Clin Lab Sci* 39, 225-283.
- 10 27. Bell, R.A., Mayer-Davis, E.J., Martin, M.A., D'Agostino, R.B., and Haffner, S.M. (2000).
- 11 Associations between alcohol consumption and insulin sensitivity and cardiovascular
- 12 disease risk factors: the Insulin Resistance and Atherosclerosis Study. *Diabetes Care* 23,
- 13 1630-1636.
- 14 28. Younis, J., Cooper, J.A., Miller, G.J., Humphries, S.E., and Talmud, P.J. (2005). Genetic
- 15 variation in alcohol dehydrogenase 1C and the beneficial effect of alcohol intake on
- 16 coronary heart disease risk in the Second Northwick Park Heart Study. *Atherosclerosis*
- 17 180, 225-232.
- 18 29. Klatsky, A.L., Gunderson, E.P., Kipp, H., Udaltsova, N., and Friedman, G.D. (2006).
- 19 Higher prevalence of systemic hypertension among moderate alcohol drinkers: an
- 20 exploration of the role of underreporting. *J Stud Alcohol* 67, 421-428.
- 21 30. (2000). *Journal of health and welfare statistics*. Volume 47. (Health and Welfare Statistics
- 22 Association), pp. 91-93.
- 23 31. Klatsky, A.L., Chartier, D., Udaltsova, N., Gronningen, S., Brar, S., Friedman, G.D., and
- 24 Lundstrom, R.J. (2005). Alcohol drinking and risk of hospitalization for heart failure with
- 25 and without associated coronary artery disease. *Am J Cardiol* 96, 346-351.
- 26 32. Lebrun, C.E., van der Schouw, Y.T., Bak, A.A., de Jong, F.H., Pols, H.A., Grobbee, D.E.,
- 27 Lamberts, S.W., and Bots, M.L. (2002). Arterial stiffness in postmenopausal women:
- 28 determinants of pulse wave velocity. *J Hypertens* 20, 2165-2172.

Table 1. Characteristics according to average daily alcohol consumption for women (n = 812)

	n	Total	Alcohol consumption (g/day)					P value ^b
			Non-drinkers	<10	10–19	20–29	30≤	
Number		812	381	145	125	66	95	
baPWV (cm/s)	812	1240 ± 176	1243 ± 178	1212 ± 163	1220 ± 164	1271 ± 196	1276 ± 181	0.022
Age	812	46.5 ± 7.1	47.4 ± 7.4	45.6 ± 6.4	46.1 ± 7.2	45.8 ± 7.5	44.8 ± 6.1	0.005
SBP (mmHg)	812	113.6 ± 15.1	112.4 ± 14.8	112.7 ± 14.4	112.1 ± 14.2	118.1 ± 17.7	118.7 ± 14.9	0.000
DBP (mmHg)	812	68.7 ± 10.0	67.5 ± 9.2	68.4 ± 10.7	67.7 ± 9.1	71.0 ± 12.2	73.3 ± 10.0	<0.0001
HR	812	59.5 ± 8.1	59.5 ± 8.1	60.0 ± 8.8	58.8 ± 7.0	59.7 ± 8.5	59.9 ± 8.1	0.779
BMI	812	21.7 ± 3.2	21.8 ± 3.4	21.8 ± 3.2	21.3 ± 2.8	21.9 ± 3.7	21.5 ± 2.9	0.685
TC (mg/dl)	812	207.5 ± 32.4	209.6 ± 32.3	206.6 ± 31.7	209.0 ± 34.3	200.3 ± 35.6	203.8 ± 28.3	0.173
TG (mg/dl) ^a	812	68.3	67.6	64.5	69.1	75.3	71.5	0.207
		(66.1, 70.6)	(64.5, 70.7)	(60.0, 69.4)	(63.0, 75.8)	(65.9, 86.2)	(64.2, 79.7)	
HDL-C (mg/dl)	812	70.2 ± 15.0	67.9 ± 14.7	69.3 ± 14.3	73.8 ± 14.5	70.2 ± 15.6	76.2 ± 15.0	<0.0001
LDL-C (mg/dl)	812	121.6 ± 30.3	126.4 ± 29.5	122.6 ± 30.7	119.2 ± 30.3	111.6 ± 30.4	111.1 ± 29.0	<0.0001
Fasting glucose (mg/dl)	812	88.1 ± 13.8	87.3 ± 11.6	88.8 ± 22.3	89.0 ± 11.2	88.9 ± 9.8	88.8 ± 10.0	0.597
Uric acid (mg/dl)	812	4.5 ± 1.0	4.3 ± 1.0	4.4 ± 1.0	4.5 ± 0.9	4.7 ± 1.0	4.7 ± 1.0	0.005
Menopause	812							0.008
Yes		301 (37.3%)	162 (42.9%)	42 (29.2%)	46 (36.8%)	26 (39.4%)	25 (26.6%)	
No		506 (62.7%)	216 (57.1%)	102 (70.8%)	79 (63.2%)	40 (60.6%)	69 (73.4%)	
Medication for diabetes	812							0.360

Yes	5 (0.6%)	2 (0.5%)	2 (1.4%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	
No	807 (99.4%)	379 (99.5%)	143 (98.6%)	125 (100%)	65 (98.5%)	95 (100%)	
Medication for hyperlipemia	812						0.249
Yes	30 (3.7%)	14 (3.7%)	7 (4.8%)	2 (1.6%)	5 (7.6%)	2 (2.1%)	
No	782 (96.3%)	367 (96.3%)	138 (95.2%)	123 (98.4%)	61 (92.4%)	93 (97.9%)	
Educational background	812						0.058
≥High school	462 (56.9%)	200 (52.5%)	92 (63.5%)	81 (64.8%)	35 (53.0%)	54 (56.8%)	
<High school	350(43.1%)	181 (47.5%)	53 (36.5%)	44 (35.2%)	31 (47.0%)	41 (43.2%)	
Frequency of exercise	812						0.498
Rarely or never	546 (67.2%)	259 (68.0%)	88 (60.7%)	82 (65.6%)	49 (74.2%)	68 (71.6%)	
1–2 times/week	193 (23.8%)	84 (22.0%)	44 (30.3%)	33 (26.4%)	12 (18.2%)	20 (21.1%)	
3 times/week or more	73 (9.0%)	38 (10.0%)	13 (9.0%)	10 (8.0%)	5 (7.6%)	7 (7.3%)	
Smoking status	812						<0.0001
Non-smoker	542 (66.8%)	276 (72.4%)	114 (78.6%)	82 (65.6%)	28 (42.4%)	42 (44.2%)	
Ex-smoker	67 (8.2%)	28 (7.4%)	7 (4.8%)	8 (6.4%)	10 (15.2%)	14 (14.7%)	
Current	203 (25.0%)	77 (20.2%)	24 (16.6%)	35 (28.0%)	28 (42.4%)	39 (41.1%)	

Variables are presented as mean ± standard deviation (SD), geometric mean (95% confidence interval [CI]), or number (percentage).

^aLog-transformed data were analyzed, and means (95% CI) were back-transformed.

^bResults of one-way ANOVA for continuous variables and the chi-square test or Fisher exact test for categorical variables are presented.

Table 2. Characteristics according to average daily alcohol consumption for men (n = 3081)

	n	Total	Alcohol consumption (g/day)					P value ^b
			Non-drinkers	<20	20–39	40–59	60≤	
Number		3081	853	709	586	418	515	
baPWV (cm/s)	3081	1350 ± 187	1329 ± 179	1320 ± 168	1345 ± 178	1380 ± 193	1405 ± 215	<0.0001
Age	3081	47.9 ± 6.9	48.2 ± 7.2	46.9 ± 7.0	47.8 ± 6.7	48.5 ± 6.5	48.5 ± 6.5	<0.0001
SBP (mmHg)	3081	121.2 ± 14.4	117.9 ± 13.5	118.3 ± 13.3	122.5 ± 14.0	124.8 ± 14.7	126.2 ± 14.8	<0.0001
DBP (mmHg)	3081	76.7 ± 10.4	74.1 ± 9.6	74.6 ± 10.0	77.9 ± 10.2	79.4 ± 10.2	80.5 ± 10.8	<0.0001
HR	3081	60.4 ± 9.3	60.7 ± 9.5	59.9 ± 9.1	60.2 ± 9.3	59.7 ± 9.0	61.5 ± 9.7	0.014
BMI	3081	23.7 ± 2.9	23.8 ± 3.1	23.5 ± 3.0	23.9 ± 2.7	23.5 ± 2.6	23.8 ± 2.8	0.149
TC (mg/dl)	3081	207.6 ± 33.5	209.3 ± 33.5	206.8 ± 33.2	207.2 ± 33.6	207.8 ± 33.9	206.1 ± 33.3	0.459
TG (mg/dl) ^a	3081	106.8 (104.8, 108.8)	105.7 (102.2, 109.3)	99.7 (96.0, 103.5)	108.9 (104.0, 114.0)	109.2 (104.2, 114.5)	114.8 (109.6, 120.3)	<0.0001
HDL-C (mg/dl)	3081	56.8 ± 14.3	51.5 ± 12.2	56.1 ± 12.8	57.5 ± 15.5	61.0 ± 14.4	62.0 ± 15.2	<0.0001
LDL-C (mg/dl)	3081	126.3 ± 31.7	133.8 ± 30.9	127.9 ± 30.0	124.1 ± 32.4	122.2 ± 31.6	117.5 ± 31.8	<0.0001
Fasting glucose (mg/dl)	3081	95.2 ± 20.8	93.4 ± 18.1	93.8 ± 19.1	94.8 ± 19.1	96.3 ± 20.5	99.8 ± 27.5	<0.0001
Uric acid (mg/dl)	3081	5.9 ± 1.2	5.7 ± 1.1	5.8 ± 1.1	5.9 ± 1.2	6.1 ± 1.2	6.0 ± 1.2	<0.0001
Medication for diabetes	3081							0.421
Yes		61 (2.0%)	22 (2.6%)	10 (1.7%)	16 (2.3%)	5 (1.2%)	8 (1.6%)	

No	3020 (98.0%)	831 (97.4%)	576 (98.3%)	693 (97.7%)	413 (98.8%)	507 (98.4%)	
Medication for hyperlipemia	3081						0.270
Yes	118 (3.8%)	39 (4.6%)	19 (3.2%)	32 (4.5%)	15 (3.6%)	13 (2.5%)	
No	2963 (96.2%)	814 (95.4%)	567 (96.8%)	677 (95.5%)	403 (96.4%)	502 (97.5%)	
Educational background	3081						<0.0001
≥High school	1317 (42.7%)	330 (38.7%)	377 (53.2%)	252 (43.0%)	168 (36.7%)	189 (36.7%)	
<High school	1765 (57.3%)	523 (61.3%)	332 (46.8%)	334 (57.0%)	250 (59.8%)	326 (63.3%)	
Frequency of exercise	3078						0.005
Rarely or never	1684 (54.7%)	495 (58.1%)	354 (50.0%)	325 (55.5%)	223 (53.4%)	287 (55.8%)	
1–2 times/week	897 (29.1%)	224 (26.3%)	240 (33.9%)	181 (30.9%)	122 (29.2%)	129 (25.1%)	
3 times/week or more	498 (16.2%)	133 (15.6%)	114 (16.1%)	80 (13.7%)	73 (17.5%)	98 (19.1%)	
Smoking status	3081						<0.0001
Non-smoker	729 (23.7%)	233 (27.3%)	234 (33.0%)	117 (20.0%)	71 (17.0%)	73 (14.2%)	
Ex-smoker	802 (26.0%)	181 (21.2%)	207 (29.2%)	163 (27.8%)	121 (29.0%)	130 (25.2%)	
Current	1551 (50.3%)	439 (51.5%)	268 (37.8%)	306 (52.2%)	226 (54.1%)	312 (60.6%)	

Variables are presented as mean ± SD, geometric mean (95% CI), or number (percentage).

^aLog-transformed data were analyzed, and means (95%CI) were back-transformed.

^bResults of one-way ANOVA for continuous variables and the chi-square test for categorical variables are presented.

Table 3. Linear regression coefficients (95% CI) for baPWV (cm/s) according to average daily alcohol consumption for women

	n	Alcohol consumption (g/day)					<i>P</i>	
		Non-drinkers	<10	10–19	20–29	30≤	Linear term	Quadratic term
Crude	812	31.15 (−2.43, 64.74)	Ref.	7.22 (−34.79, 49.23)	58.61 (7.50, 109.72)	63.83 (18.40, 109.27)	0.401	0.083
Model 1	812	24.24 (2.70, 45.78)	Ref.	11.22 (−15.62, 38.06)	18.09 (−14.69, 50.86)	23.56 (−5.70, 52.83)	0.169	0.129
Model 2	812	26.63 (5.60, 47.66)	Ref.	6.28 (−20.09, 32.65)	14.58 (−17.68, 46.83)	17.61 (−11.55, 46.78)	0.046	0.058
Model 3	812	26.49 (5.35, 47.63)	Ref.	4.78 (−21.69, 31.25)	11.09 (−21.70, 43.87)	13.99 (−15.75, 43.73)	0.032	0.056

Model 1: Adjusted for age, SBP, and HR.

Model 2: Model 1+ adjusted for menopause, medication for diabetes, medication for hyperlipemia, BMI, TC, log TG, HDL-C, and FBS.

Model 3: Model 2+ adjusted for lifestyle factors (education, exercise, and smoking).

Table 4. Linear regression coefficients (95% CI) for baPWV (cm/s) according to average daily alcohol for men

	n	Alcohol consumption (g/day)					<i>P</i>	
		Non-drinkers	<20	20–39	40–59	60≤	Linear term	Quadratic term
Crude	3081	−15.33 (−34.78, 4.13)	−24.49 (−44.74, −4.24)	Ref.	35.29 (12.08, 58.51)	59.94 (38.04, 81.84)	<0.0001	0.4221
Model 1	3081	13.71 (0.04, 27.38)	13.52 (−0.67, 27.70)	Ref.	15.65 (−0.55, 31.85)	23.11 (7.79, 38.43)	0.702	0.042
Model 2	3081	15.72 (2.17, 29.27)	13.85 (−0.01, 27.72)	Ref.	11.24 (−4.59, 27.08)	17.65 (2.56, 32.73)	0.205	0.030
Model 3	3078	15.38 (1.80, 28.95)	15.45 (1.50, 29.41)	Ref.	11.34 (−4.47, 27.16)	17.69 (2.57, 32.38)	0.219	0.036

Model 1: Adjusted for age, SBP, and HR.

Model 2: Model 1+ adjusted for medication for diabetes, medication for hyperlipemia, BMI, TC, log TG, HDL-C, and FBS.

Model 3: Model 2+ adjusted for lifestyle factors (education, exercise, and smoking).

Table 5. Linear regression coefficients (95% CI) for baPWV (cm/s) according to average daily alcohol consumption by age for men

		Alcohol consumption (g/day)					<i>P</i>	
	<i>n</i>	Non-drinkers	<20	20–39	40–59	60≤	Linear term	Quadratic term
<45		277	281	196	121	156		
Crude	1031	−14.50 (−39.94, 10.95)	−13.28 (−38.65, 12.09)	Ref.	19.02 (−12.49, 50.54)	40.14 (10.89, 69.39)	0.002	0.740
Model 1	1031	8.29 (−11.49, 28.06)	8.26 (−11.36, 27.88)	Ref.	15.05 (−9.19, 39.23)	1.82 (−20.85, 24.48)	0.800	0.940
Model 2	1031	13.79 (−6.13, 33.72)	11.30 (−8.23, 30.82)	Ref.	11.98 (−12.09, 36.05)	−3.05 (−25.69, 19.60)	0.244	0.857
Model 3	1031	12.73 (−7.25, 32.71)	12.19 (−7.47, 31.86)	Ref.	12.42 (−11.61, 36.46)	−5.54 (−28.37, 17.28)	0.267	0.938
45≤		576	428	390	297	359		
Crude	2050	−17.26 (−42.23, 7.71)	−20.57 (−47.23, 6.08)	Ref.	35.17 (5.85, 64.50)	63.73 (35.88, 91.57)	<0.001	0.540
Model 1	2050	22.06 (3.79, 40.34)	15.55 (−3.90, 35.01)	Ref.	16.25 (−5.11, 37.61)	36.49 (16.21, 56.78)	0.389	0.003
Model 2	2050	20.46 (2.47, 38.44)	14.57 (−4.28, 33.43)	Ref.	13.56 (−7.17, 34.29)	32.29 (12.44, 52.14)	0.352	0.004
Model 3	2047	19.76 (1.72, 37.80)	16.79 (−2.26, 35.84)	Ref.	13.63 (−7.09, 34.35)	32.87 (12.97, 52.76)	0.390	0.005

Model 1: Adjusted for SBP, and HR.

Model 2: Model 1+ adjusted for medication for diabetes, medication for hyperlipemia, BMI, TC, log TG, HDL-C, and FBS.

Model 3: Model 2+ adjusted for lifestyle factors (education, exercise, and smoking).

