

Association of Alcohol Consumption with Increase in Aortic Stiffness: A 9-Year Longitudinal Study in Middle-Aged Japanese Men

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Abstract: A 9-year longitudinal study was performed to prospectively examine the association of alcohol consumption with development of aortic stiffness in 1121 aortic stiffness-free [aortic pulse wave velocity (PWV) of less than 8.0 m/sec] Japanese men aged 35 to 59 years without definite hypertension, hypercholesterolemia, or diabetes. 274 men developed aortic stiffness (aortic PWV of 8.0 m/sec or more) during 8872 person-years follow-up. After controlling for potential predictors of aortic stiffness, the relative risk for increased aortic stiffness compared with non-drinkers was 1.01 [95% confidence interval (CI): 0.62–1.64] for those who drank 0.1 to 22.9 g/day of ethanol, 1.71 (95% CI: 1.12–2.60) for those who drank 23.0 to 45.9 g/day of ethanol, 1.79 (95% CI: 1.18–2.71) for those who drank 46.0 to 68.9 g/day of ethanol, and 2.09 (95% CI: 1.35–3.26) for those who drank 69.0 or more g/day of ethanol (P for trend < 0.001). These results suggest that alcohol consumption is closely associated with development of aortic stiffness.

Key words: Pulse wave velocity, Aortic stiffness, Alcohol, Longitudinal study, Middle-age, Japanese men

Many epidemiological studies suggest a U- or J-shaped association between alcohol consumption and coronary heart disease (CHD)¹. Although it has been suggested that moderate alcohol consumption slows atherosclerosis by beneficial effects on lipid metabolism, thrombogenesis and fibrinolytic activity, the relation between alcohol consumption and a lower risk for CHD appears to be more complex^{2, 3}; alcohol induces hypertension and is a risk factor for aneurysmal degeneration. As for the effect of alcohol consumption on aortic stiffness or decreased aortic compliance, evidence linking alcohol consumption and aortic stiffness is very few. One cross sectional study among Japanese Americans reported that the risk for high aortic

pulse wave velocity (PWV) as an aortic distensibility index was lower among current drinkers and ex-drinkers than among non-drinkers⁴. However, other longitudinal study among Japanese men reported that the incidence of increased aortic PWV was not related to alcohol intake⁵. These inconclusive results may have been resulted in part from lifestyle differences in the study populations but also may have been strongly influenced by different methods used to investigate the association between alcohol intake and aortic PWV. In addition, subjects with risk factors for aortic PWV such as hypertension, dyslipidemia, or diabetes were enrolled in these studies, and these confounders may have influenced their results. Therefore, it is necessary to conduct a longitudinal study in subjects without hypertension, dyslipidemia, or diabetes at baseline to clarify the relation

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between alcohol intake and risk for development of aortic stiffness. In this follow-up study, we attempted to prospectively investigate the association of alcohol intake with development of aortic stiffness on the basis of the measurement of aortic PWV in middle-aged Japanese male office workers without definite hypertension, hypercholesterolemia, or diabetes.

The surveillance population consisted of 1640 Japanese male office workers 35 to 59 years of age in May 1990 in T Corporation, Osaka. All the participants were architects, research workers, or clerks and no one engaged in physical or muscular labor. Of 1640 potential participants, 182 (11.1%) showed aortic PWV of 8.0 m/sec or more at entry. Comparing aortic PWV values and postmortem pathological examination, disorders of the internal elastic plate in the intima of vessels, pathological intima hypertrophy and atheroma, and decreased elastic fibers in the media were found to be associated with aortic PWV of 8 m/sec or more⁶. Therefore, these 182 men who had aortic PWV of 8.0 m/sec or more were excluded from this study as those who already had aortic stiffness. Furthermore, 308 men with hypertension [systolic blood pressure (SBP) \geq 160 mmHg and/or diastolic blood pressure (DBP) \geq 95 mmHg or receipt of medication for hypertension], hypercholesterolemia (serum total cholesterol level \geq 260 mg/dl or receipt of medication for dyslipidemia) or diabetes mellitus based on the new criteria (fasting plasma glucose level \geq 126 mg/dl or receipt of medication for diabetes) were excluded from the study to avoid confounding effects of hypertension, dyslipidemia, or diabetes on arterial stiffness. Thus, the baseline population consisted of 1150 men. We also excluded 29 men who did not participate in consecutive annual health examinations during follow-up. The final study population for analysis therefore consisted of 1121 men. Men in whom aortic PWV values of 8.0 m/sec or more were found during repeated surveys through May 1999 were defined as incidental cases of aortic stiffness.

Annual health examinations included a questionnaire on alcohol intake and smoking, anthropometric measurements, blood pressure measurement, collection of blood samples for laboratory analysis and the measurement of aortic PWV. Data on alcohol intake and smoking habits were obtained by interview. An interviewer assessed the usual weekly intake of alcohol in a volume unit of "go" (a traditional Japanese unit of measurement for "Sake", corresponding to 23 g of ethanol), which were converted to grams of ethanol per day. One "go" is 180 ml of "Sake", and it corresponds to one bottle (663 ml) of beer, two single shots (75 ml) of whisky, or two glasses (180 ml) of wine. The questionnaire asked

about smoking habits (never, past, or current smoker); past or current smokers were asked about the number of cigarettes smoked daily and the duration of smoking in years. In this study, past and never smokers were combined, and the number of cigarettes smoked daily was used in the analysis. Body mass index (BMI) was used as a measure of overall obesity and was calculated as body weight/height² (kg/m²). After a 5-minute rest in a quiet room, SBP and DBP were measured on the right arm by using a standard mercury sphygmomanometer. Blood samples were drawn from an antecubital vein. The Olympus AU-5000 spectrophotometer was used to measure serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride and fasting plasma glucose. The hematocrit was determined by using Sysmex E-4000 autoanalyzer (Toa Medical Electronics Co, Ltd., Tokyo, Japan).

Aortic PWV of each participant was measured in the supine position after a 5-minute bed rest by using a pulse-wave velocimeter (model PWV-100, Fukuda Denshi Corporation, Tokyo, Japan) from 1990 to 1999. Amorphous sensors were placed on the skin at the right femoral and left carotid arteries to record pulse waves. Heart sounds S1 and S2 were detected by a microphone set on the right edge of the sternum at the second intercostal space. Electrocardiogram monitoring was performed with electrodes placed on the right and left arms and on the right leg. The PWV meter measured the time intervals between pulse waves at carotid and femoral sites (T) and between S2 and the notch of the carotid pulse wave (Tc). PWV of the aorta was calculated as $1.3 L / (T + Tc)$, where aortic PWV is measured in meters per second and L is the measured distance between the carotid and femoral probes⁷. The actual distance between the aortic orifice and the femoral site was calculated as 1.3 L. Because (T + Tc), the time for the pulse waves to travel from the aortic orifice to the femoral artery, is dependent on blood pressure, aortic PWV values were standardized for a diastolic pressure of 80 mmHg. The coefficients of variation for aortic PWV were no more than 5% from 1990 to 1999.

As for analytical procedures, one-way analysis of variance and the chi-square test were used to analyze the statistical differences among characteristics of participants at enrollment according to alcohol intake. For each participant, person-years of follow-up were calculated by using the date of the initial examination and the date of diagnosis of increased aortic stiffness or the date of follow-up (the tenth examination), or the date of last registration in T Corporation, Osaka. Those who had been transferred to another locality or had retired during the follow-up period have censored observation times as do those members of the cohort who

Table 1. Baseline characteristics of 1121 aortic stiffness-free Japanese male office workers, according to alcohol intake

Characteristics	Non-drinkers (n=195)	Current drinkers (g/day of ethanol)				P value
		0.1–22.9 (n=184)	23.0–45.9 (n=248)	46.0–68.9 (n=306)	≥ 69.0 (n=188)	
Age (years)	46.2 (6.8)	43.5 (5.1)	44.4 (5.4)	43.6 (4.6)	44.0 (4.8)	< 0.001
Pulse wave velocity (m/sec)	7.26 (0.37)	7.19 (0.41)	7.23 (0.40)	7.24 (0.39)	7.28 (0.34)	0.262
Body mass index (kg/m ²)	23.0 (2.5)	23.3 (2.6)	23.0 (2.5)	23.1 (2.6)	23.2 (2.4)	0.727
Systolic blood pressure (mmHg)	125.0 (12.3)	125.2 (13.4)	127.0 (12.5)	127.5 (12.0)	128.3 (12.0)	0.016
Diastolic blood pressure (mmHg)	77.4 (8.6)	78.1 (9.6)	78.8 (8.5)	79.1 (8.6)	79.3 (8.0)	0.151
Total cholesterol (mg/dl)	197.9 (28.5)	198.7 (29.8)	194.7 (29.2)	194.8 (28.4)	198.7 (29.9)	0.347
High-density lipoprotein cholesterol (mg/dl)	54.7 (13.2)	55.8 (13.6)	57.2 (12.3)	58.7 (13.6)	59.3 (13.5)	< 0.001
Triglycerides (mg/dl)	126.0 (94.5)	125.9 (84.8)	120.1 (76.0)	120.9 (75.8)	132.8 (85.7)	0.505
Fasting plasma glucose (mg/dl)	92.3 (9.2)	91.8 (10.0)	90.8 (9.8)	92.0 (9.4)	91.4 (10.4)	0.495
Hematocrit (%)	45.9 (2.6)	46.4 (2.4)	46.1 (3.1)	46.0 (2.8)	46.2 (2.7)	0.601
Cigarette smoking (cigarettes/day)	13.4 (17.7)	17.3 (16.6)	17.4 (14.0)	21.5 (16.8)	25.0 (17.0)	< 0.001
Current smokers (%)	33.3	45.7	48.8	54.6	64.4	< 0.001

Values are expressed as means (standard deviations) or %.

were still in T Corporation, Osaka, at the end of the follow-up. The follow-up rate was 95.7% of the total potential person-years of follow-up. The method of Kaplan-Meier was used to estimate the cumulative incidence of increased aortic stiffness according to alcohol intake, and the log-rank test was used to assess the significance of the unadjusted difference among the incidence curves. Cox proportional hazards models were used to evaluate the association between alcohol consumption and development of aortic stiffness. Data were adjusted first for age alone, then for the following multiple covariates: age, BMI, cigarette smoking, DBP, total cholesterol level, HDL cholesterol level, triglyceride level, fasting plasma glucose level and hematocrit. In the statistical analyses, the logarithm for the triglyceride was used because of the non-gaussian distribution of the frequency for this variable. Potential confounding factors except cigarette smoking were treated as continuous variables and cigarette smoking was graded as 1 (none) or as quartile 1 (grade of 2) to quartile 4 (grade of 5) for smokers. The linear trends in risks were evaluated by using the median value for each category of alcohol consumption. All reported P values are two-tailed; those less than 0.05 were considered statistically significant.

Table 1 shows the baseline characteristics of the study sample according to alcohol intake. Means of age, SBP, HDL cholesterol level, and the number of cigarettes smoked daily and the percentage of participants who smoked cigarettes daily differed significantly by the status of alcohol intake. Non-drinkers were older than current drinkers. Means of SBP, HDL cholesterol level, the number of cigarettes smoked daily and the percentage of those who smoked

cigarettes daily increased as alcohol consumption increased. DBP tended to increase as alcohol consumption increased, but there were no significant differences among five groups. Means of BMI, total cholesterol level, triglyceride level, fasting plasma glucose level and hematocrit did not differ significantly among five groups.

During 9 years of follow-up representing 8872 person-years, 274 men developed aortic stiffness (Fig. 1 and Table 2). The curves for the incidence of increased aortic stiffness for the five subclasses of alcohol intake differed significantly ($P=0.030$). The age-adjusted relative risk for increased aortic stiffness compared with non-drinkers was 1.05 (95% CI: 0.65–1.70) for those who drank 0.1 to 22.9 g/day of ethanol, 1.60 (95% CI: 1.06–2.41) for those who drank 23.0 to 45.9 g/day of ethanol, 1.89 (95% CI: 1.26–2.82) for those who drank 46.0 to 68.9 g/day of ethanol, and 2.28 (95% CI: 1.50–3.48) for those who drank 69.0 or more g/day of ethanol. The test for trend across increasing categories of alcohol consumption was statistically significant ($P<0.001$). The respective multivariate-adjusted relative risks for increased aortic stiffness compared with non-drinkers were 1.01 (95% CI: 0.62–1.64), 1.71 (95% CI: 1.12–2.60), 1.79 (95% CI: 1.18–2.71), and 2.09 (95% CI: 1.35–3.26) (P for trend < 0.001). These results suggest that alcohol is an important risk factor for development of aortic stiffness in middle-aged Japanese men and that a reduction in alcohol intake might prove to be a factor in achieving the primary prevention of development of aortic stiffness for this population.

The mechanism of how alcohol intake increases the risk for aortic stiffness remains to be elucidated. Laboratory studies^{8,9} have shown that large intakes of alcohol associate

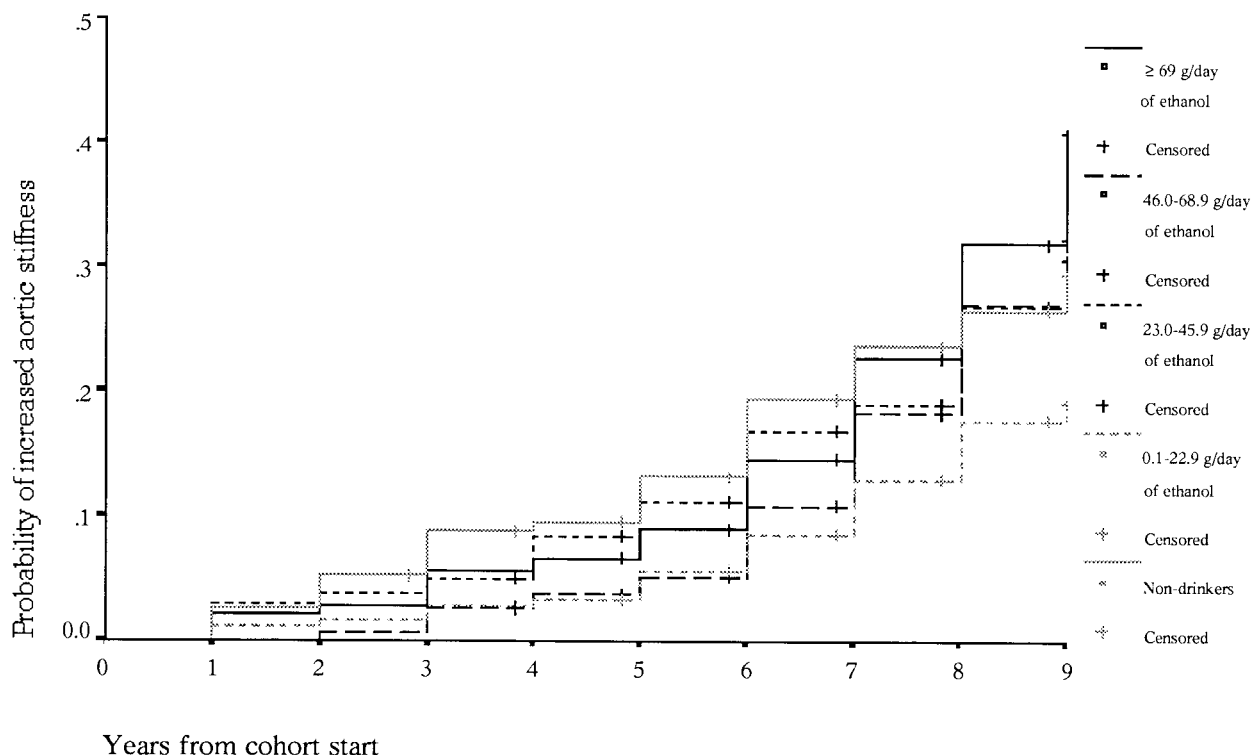


Fig. 1. Cumulative incidence of increased aortic stiffness among 1121 Japanese male office workers during 9 years of follow-up, according to alcohol intake.

Table 2. Alcohol intake and risk of increased aortic stiffness among 1121 Japanese male office workers during 9 years of follow-up

	Non-drinkers	Current drinkers (g/day of ethanol)				P for trend*
		0.1–22.9	23.0–45.9	46.0–68.9	≥ 69.0	
Cases	41	31	62	81	59	
Person-years	1349	1538	1966	2526	1494	
Rate per 1000 person-years	30.4	20.2	31.5	32.1	39.5	
Age-adjusted relative risk	1.00	1.05	1.60	1.89	2.28	< 0.001
(95% CI)	(Reference)	(0.65–1.70)	(1.06–2.41)	(1.26–2.82)	(1.50–3.48)	
Multivariate-adjusted relative risk†	1.00	1.01	1.71	1.79	2.09	< 0.001
(95% CI)	(Reference)	(0.62–1.64)	(1.12–2.60)	(1.18–2.71)	(1.35–3.26)	

*The test for trend is calculated across increasing categories of alcohol intake. †Controls for age, pulse wave velocity, body mass index, diastolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, fasting plasma glucose level, hematocrit and cigarette smoking at study entry.

with increased low-density lipoprotein (LDL) oxidation and that high titers of antibodies against oxidized LDL associate with accelerated progression of atherosclerosis. Acetaldehyde, which is an immediate metabolic product of alcohol and appears to be a particularly potent toxin, is likely to contribute to ethanol-related oxidative stress inside vessels¹⁰. An experimental study¹¹ has recently reported that long-term alcohol consumption upregulates matrix

metalloproteinase-2 (MMP-2), which is a member of the MMPs family with specificity for type IV collagen and elastin, and that the increased MMP-2 activity possesses elastase activity and is capable of degrading aortic elastic fibers. Local increase of MMP-2 activity induced by alcohol consumption may lead to an increase in breakdown of collagen and extracellular matrix and might be responsible for aortic stiffness. Furthermore, ethanol influences a diverse

range of cell surface receptors like GABA_A receptors, opioid receptors, and epidermal growth factor receptor¹²⁻¹⁴). At the level of vasculature, the endothelium actively participates in maintaining the vascular tone by controlling its own production of various vasoactive factors including nitric oxide, prostacyclin, and endothelin¹⁵). Thus, perturbation of metabolisms and the endothelial cell-derived vasoactive factors due to alcohol consumption might also be responsible for aortic stiffness.

Our results suggest that alcohol consumption is closely associated with risk for increase in aortic stiffness. However, drinkers were less healthy than non-drinkers in several other ways that might explain their higher risk for increase in aortic stiffness: drinkers had higher levels of blood pressure and smoked more cigarettes daily. Furthermore, aortic PWV is an indirect marker of aortic stiffness and is affected by various hemodynamic factors such as blood pressure. Further investigation is needed to clarify the causal relation between alcohol consumption and risk for aortic stiffness.

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