Alcohol Consumption and Mortality from Aortic Disease among Japanese Men: The Japan Collaborative Cohort Study

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Background and aims: Only a few population-based prospective studies have examined the association between alcohol consumption and abdominal aortic aneurysm, and the results are inconsistent. Moreover, no evidence exists for aortic dissection. We examined the effect of alcohol consumption on risk of mortality from aortic diseases.

Method: A total of 34,720 men from the Japan Collaborative Cohort study, aged 40 to 79 years, without history of cardiovascular disease and cancer at baseline 1988 and 1990 were followed up until the end of 2009 for their mortality and its underlying cause. Hazard ratios of mortality from aortic diseases were estimated according to alcohol consumption categories of never-drinkers, ex-drinkers, regular drinkers of ≤30 g, and >30 g ethanol per day.

Results: During the median 17.9-year follow-up period, 45 men died of aortic dissection and 41 men died of abdominal aortic aneurysm. Light to moderate drinkers of ≤30 g ethanol per day had lower risk of mortality from total aortic disease and aortic dissection compared to never-drinkers. The respective multivariable hazard ratios (95% confidence intervals) were 0.46 (0.28–0.76) for total aortic disease and 0.16 (0.05–0.50) for aortic dissection. Heavy drinkers of >30 g ethanol per day did not have reduced risk of mortality from total aortic disease, albeit had risk variation between aortic dissection and abdominal aortic aneurysm.

Conclusion: Light to moderate alcohol consumption was associated with reduced mortality from aortic disease among Japanese men.

Keywords: Epidemiology, Abdominal aortic aneurysm, Aortic dissection, Mortality, Alcohol, Risk factor

Light to moderate alcohol consumption has a protective effect against the development of cardiovascular diseases such as ischemic stroke and coronary artery disease [1]. However, previous observational studies reported inconsistent results with positive [2], inverse [3], and U-shaped [4] relationships between alcohol consumption and the risk of abdominal aortic aneurysm. To our knowledge, there is no prospective evidence on the risk of abdominal aortic aneurysm among nonwhite populations or on the risk of aortic dissection in either whites or nonwhites. We examine the association of alcohol consumption with mortality from aortic disease among male participants in a large population-based cohort study.

Although the etiologies of aortic diseases remain unclear, advancing age, smoking, and hypertension are reported risk factors for both aortic aneurysm and dissection [2,4–6]. Thoracic aortic aneurysm and aortic dissection are characterized by minimal plaque formation [7,8], whereas abdominal aortic aneurysm is usually comorbid with severe atherosclerosis [6,9]. Chronic alcohol consumption raises blood pressure [10], while light to moderate alcohol consumption reduces atherosclerosis formation [11]. Therefore, the effect of alcohol consumption on aortic dissection and abdominal aortic aneurysm may be different.

Materials and methods

The Japan Collaborative Cohort (JACC) Study is a population-based cohort study with

baseline survey conducted from 1988 to 1990 in 45 areas in Japan. Details of the study have been described elsewhere [13,14]. In total, 110,585 eligible participants (46,395 men and 64,190 women) aged 40 to 79 years were registered in the study. Baseline information was collected by a self-administered questionnaire. Additionally, about 5 years after the baseline survey, an interim survey regarding lifestyle changes was conducted in 31 areas. Informed consent was obtained before administration of the questionnaire from most participants in written or verbal form. In some communities, informed consent was obtained from the local community leader based on the guidelines of the Council of International Organizations of Medical Science [15]. The present study was approved by the ethics committees of Nagoya University and Osaka University.

Of the 46,395 male participants, we excluded 2574 men because of a history of cancer, stroke, or myocardial infarction and 9101 men because of missing information regarding drinking habits. In total, 34,720 men were included in this study. We limited our analysis to male participants because the proportion of current drinkers was 15% among female participants and the number of deaths from aortic disease among them was small (n = 6).

Date of mortality and its underlying cause were followed up on the death certificate annually or biennially by inquiring to the Ministry of Internal Affairs and Communication of Japan.

Moving-outs from the study area were followed in collaboration with local governments in each area. In most of the areas, the subjects' mortality was followed up until the end of 2009 with the exceptions of 4 areas until 1999, 4 areas until 2003, and 2 areas until 2008. The underlying cause of death was recorded using the International Classification of Diseases version 10 (ICD 10). Aortic dissection corresponds to ICD-10 code I710, and aortic aneurysm corresponds to I711 to I719.

Baseline information collected by self-administrated questionnaire included alcohol drinking status and its consumption; demographic characteristics; histories of hypertension, diabetes mellitus, and other chronic disease; and lifestyle factors such as smoking, diet, sports, and walking habit.

Drinking status was inquired to classify participants into never-, ex-, and regular drinkers. Alcohol consumption was estimated from frequency (occasions per week), beverage type, and average amount on one occasion for regular drinkers. Beverage type was asked by a multiple choice question with items of sake (filtrate of fermented rice), shochu (beverage distilled from fermented barley, potatoes, buckwheat, or rice), beer, whisky, or wine. The daily amount of alcohol consumption (g per day) was calculated as the product of the frequency (occasion per week) and amount per occasion divided by seven.

Statistical Analysis

The subjects were classified into four groups according to their drinking status and amount of alcohol consumption (never-drinkers, ex-drinkers, and current drinkers who consume ≤30 and >30 g ethanol per day). Ex-drinkers were those who had had drinking habit but quit until the baseline survey. The age-adjusted mean value and prevalence of risk factors for each category were calculated by a general linear model. The P value for trend was derived from linear regression for continuous variables and logistic regression for prevalence. Hazard ratios of mortality from aortic diseases were estimated with reference to never-drinkers using a Cox proportional hazard model. Covariates in the model were age at baseline (continuous), history of hypertension and diabetes mellitus (yes or no), smoking status (nonsmokers, ex-smokers, and <20 and ≥20 cigarettes per day), body mass index (quintile). Proportions of missing information were 4.4% for body mass index, 9.6% for history of hypertension, 11.6% for history of diabetes mellitus, and 0% for smoking habit. Those with missing data in the covariates were kept in the analyses by assigning them a value for missing category. Because the number of events per variable in the Cox proportional hazards model should not exceed 7 or 10 for stable estimation [16], we performed multivariable analyses by adding each covariate one by one.

The beverage-specific association between alcohol consumption and mortality from total aortic disease was examined for Japanese traditional alcohol beverage sake and shochu, which accounted for 35% of the beverage consumed in the study population.

Changes in the alcohol consumption were assessed according to the result of baseline and the 5-year interim survey. Proportions of respondents in the same category, the adjacent category, and the reversal category was calculated. The adjacent category consists of those reported themselves as never drinker at baseline and regular drinker with ≤30 g ethanol per day at the interim surveys; regular drinker with ≤30 g per day at baseline and never drinker or regular drinker of >30 g per day at the interim surveys; and regular drinker of >30 g per day at baseline and regular drinker of ≤30 g per day at the interim surveys. The reversal category consists of those reported never drinker at baseline but regular drinker of >30 g per day at the interim survey, and regular drinker of >30 g per day at baseline but never drinker at the interim survey. The former drinker category was excluded in the definition of these drinking habit change because of they may refrain from alcohol because of their ill health condition.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC). Two-tailed p values of <0.05 were considered statistically significant.

Results

Current drinkers were younger, more hypertensive, and heavier smokers than were never-drinkers. Ex-drinkers were older, more hypertensive, lighter smokers, and more likely to have history of diabetes mellitus than never drinkers and current drinkers (Table 1).

During the follow-up of 530,542 person-years, we documented 117 deaths from aortic disease: 45 aortic dissections, 24 thoracic aortic aneurysms, 41 abdominal aortic aneurysms, 3 thoracoabdominal aortic aneurysms, and 4 aortic aneurysms of an unspecified site. The crude mortality rate of total aortic disease was 22 per 100,000 person-years.

Light to moderate alcohol consumption (≤30 g ethanol per day) was associated with reduced risk of mortality from total aortic disease and aortic dissection with multivariable hazard ratios (95% confidence interval [CI]) of 0.46 (0.28–0.76) and 0.16 (0.05–0.50), respectively (Table 2). Heavy drinkers of >30 g ethanol per day did not have lower risk of mortality from total aortic disease, although they tended to have lower risk of mortality from abdominal aortic aneurysm but not from aortic dissection (Table 2). The adjustments for each covariate showed similar results to the age-adjusted and multivariable models (see online supplementary table 1).

History of hypertension was associated with increased mortality from aortic dissection with multivariable hazard ratio (95% CI) of 4.18 (2.21–7.89), but not with abdominal aortic aneurysm with multivariable hazard ratio of 1.47 (0.70–3.11). The multivariable hazard ratios (95% CI) of mortality from thoracic aortic disease (aortic dissection or thoracic aortic aneurysm) were 0.34 (0.15–0.73) for those who consumed ≤30 g ethanol per day and 0.83 (0.45–1.56) for >30 g compared to never-drinkers.

The association between alcohol consumption and mortality from total aortic disease did not alter when the analysis was restricted to 15,889 participants who reported that they drunk sake only or shochu only. The multivariable hazard ratios (95% CI) of mortality from total aortic disease were 0.45 (0.22-0.95) for those drunk ≤30 g ethanol per day and 0.63 (0.34-1.17) for >30 g compared to never drinkers.

Among the 10,187 (40%) subsample participants who completed the alcohol questionnaire at baseline and the 5-year followed-up surveys, the proportions of the same category, the adjacent category, and the reversal category of alcohol consumption were 72%, 20%, and 0.3%, respectively.

Discussion

According to the long-term prospective study of 34,720 Japanese men, light to moderate alcohol consumption was associated with lower mortality from total aortic diseases and aortic dissection compared to never drinking, while heavy drinking was associated with no reduced risk, showing a reverse J-shaped relationship. This is the first population-based prospective study to examine the effect of alcohol consumption on aortic dissection. Furthermore, the sample size of the JACC Study is one of the largest among population-based cohort studies of aortic disease worldwide.

Our finding is consistent with a cohort study of 48,850 Swedish men that found an inverse association between moderate consumption and risk of rupture or repair of abdominal aortic aneurysm with a diameter of >55 mm with a hazard ratio (95% CI) of 0.78 (0.62–0.97) for those who consumed 10 glasses per week (equivalent to 17.1 g ethanol per day) compared with those who consumed 1 glass per week [3]. On the contrary, the Health Professional Follow-up Study showed a positive association between alcohol consumption and increased risk of incident abdominal aortic aneurysm (dilated aorta of >30 mm, repair, or mortality) of 39,352 men [2]. The discrepancy from the result of Swedish study could be due to the lower cut-off value to define abdominal aortic aneurysm cases in the Health Professional Follow-up Study, in which 55% of the cases were <50 mm in diameter. The present study examined

mortality as the endpoint, which may encompass only large aneurysms.

The differential effect of heavy alcohol consumption on aortic dissection and abdominal aortic aneurysm could be explained essentially by its effect on hypertension and atherosclerosis. Atherosclerosis is almost always present with abdominal aortic aneurysms [6], but generally absent in thoracic aortic aneurysm [7] and aortic dissection [8]. Although atherosclerosis may not be a single causal pathology of abdominal aortic aneurysm [17], our finding of a protective effect of heavy drinking against mortality from abdominal aortic aneurysm may be in part due to an antiatherogenic effect of ethanol through improved lipid profiles such as increased high-density lipoprotein cholesterol and decreased low-density lipoprotein cholesterol concentrations [18]. This notion is supported by the finding from a meta-analysis of 10 observational studies that reported a reduced growth rate of abdominal aortic aneurysm among patients receiving statin [19]**.** This antiatherogenic effect of alcohol consumption may as well explain the reduced risk of mortality from aortic dissection in the present study since penetrating atherosclerotic ulcer is one of the cause of initial tear of aortic dissection. On the other hand, hypertension would be more strongly related to the development of aortic dissection than abdominal aortic aneurysm as observed in the present study.

Other mechanisms may include the effects of alcohol consumption on systemic inflammation, matrix metalloproteinase (MMP) activity, thrombus formation, and serum adipocytokine levels. Light to moderate alcohol consumption has been associated with lower levels of inflammation markers including interleukin-6 (an upstream maker of C-reactive protein or fibrinogen) [20,21], whose receptor is an important pathway for the development of abdominal aortic aneurysm [22]. Furthermore, moderate alcohol consumption reduced platelet aggregation [23] and circulating MMP-2 activity [24], enhanced fibrinolysis [25], and increased adiponectin level [18], all of which contribute to the reduced risk of aortic diseases [26–28] . Although the causality cannot be determined from an observational study, our findings could be generalized to middle-aged men of other ethnicities according to these mechanisms.

This study has some limitations. First, we identified cases of aortic disease through death certificates, which may be liable to misclassification. However, computed tomography has been disseminated throughout Japan even in local hospitals since the 1980s, which would likely ensure sufficient diagnostic accuracy in this study. Second, drinking status and alcohol consumption were assessed only at the baseline survey. However, among the 40% of the participants who reported their drinking habit at the 5-year interim survey, 72% did not change their drinking habit and 20% changed slightly, and less than 1% changed their habit

between non-drinking and heavy drinking. Therefore, the observed association could have been weaker than the real association because changes in drinking status and alcohol consumption during follow-up would weaken the real association. Third, the present study lacks biomedical measurements at the baseline and histories of hypertension and diabetes mellitus were based on self-reports. However, the validity of self-reports for history of hypertension and diabetes mellitus is reported to be high with sensitivity and specificity of more than 70% [29]. Fourth, the information of hypercholesterolemia or blood lipid levels was not collected in the present study. Although alcohol consumption may be somewhat related to total and LDL-cholesterol levels, the association between alcohol consumption and incident abdominal aortic aneurysm in the Health Professional Study was not attenuated by the adjustment for hypercholesterolemia [2]. Therefore, the lack of history of hypercholesterolemia was unlikely to affect the overall result in the present study. Fifth, the misdiagnosis between aortic dissection and rupture of thoracic aortic aneurysm is expected because thoracic aortic aneurysm can result in dissection [30] and aortic dissection can lead to rupture [31]. However, the lumping of these diseases together showed a similar U-shaped relationship. Sixth, the small number of cases may have introduced an overfitting after adjustments for the 5 sub-divided covariates. However, the one-by-one adjustments for each confounder showed similar results with the multivariable adjusted model. Seventh, the potentially differential effect of beverage types could not be assessed in the present study due

to small number of cases. Stackelberg et al. showed that beer in men and wine in women were specifically associated with decreased risk of abdominal aortic aneurysm and explained those associations in part by antioxidants contained in these beverages [3]. However, such effects of antioxidants would be small in the present study since the proportions of those drinking beer and wine were 19% and 6% respectively. There was similar reduced risk of mortality from total aortic disease by light to moderate drinking among those who consumed sake or shochu only. Interaction between the beverage type and the individual genetic factor such as alcohol dehydrogenase phenotypes is an area of future investigation [32,33].

In conclusion, light to moderate alcohol consumption was associated with lower mortality from aortic disease compared with never-drinking, while heavy drinking was associated with no reduced risk. Light to moderate alcohol consumption may be beneficial for the prevention of aortic disease mortality, like for ischemic stroke and coronary heart disease.

Conflicts of interest

None.

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Author contributions

AT was involved in the design of study as the principal investigator. HI was also involved in the design of study. KY, HY, NT, AT, and HI conducted the survey. TS planned and conducted data analysis and drafted the manuscript. All authors were involved in interpretation of the results, revision of the manuscript and approved the final version of the manuscript.

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Appendix

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References

[1] Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 2011;342:d671. doi:10.1136/bmj.d671.

[2] Wong DR, Willett WC, Rimm EB. Smoking, hypertension, alcohol consumption, and risk of abdominal aortic aneurysm in men. Am J Epidemiol 2007;165:838–45. doi:10.1093/aje/kwk063.

[3] Stackelberg O, Björck M, Larsson SC, Orsini N, Wolk A. Alcohol consumption, specific alcoholic beverages, and abdominal aortic aneurysm. Circulation 2014;130:646–52. doi:10.1161/CIRCULATIONAHA.113.008279.

[4] Törnwall ME, Virtamo J, Haukka JK, Albanes D, Huttunen JK. Life-style factors and risk for abdominal aortic aneurysm in a cohort of Finnish male smokers. Epidemiology 2001;12:94–100.

[5] Strachan DP. Predictors of death from aortic aneurysm among middle-aged men: The Whitehall study. Br J Surg 1991;78:401–4. doi:10.1002/bjs.1800780407.

[6] Reed D, Reed C, Stemmermann G, Hayashi T. Are aortic aneurysms caused by atherosclerosis? Circulation 1992;85:205–11. doi:10.1161/01.CIR.85.1.205.

[7] Achneck H, Modi B, Shaw C, Rizzo J, Albornoz G, Fusco D, et al. Ascending thoracic aneurysms are associated with decreased systemic atherosclerosis. Chest 2005;128:1580–6. doi:10.1378/chest.128.3.1580.

[8] Larson EW, Edwards WD. Risk factors for aortic dissection: A necropsy study of 161 cases. Am J Cardiol 1984;53:849–55.

[9] Johnsen SH, Forsdahl SH, Singh K, Jacobsen BK. Atherosclerosis in abdominal aortic aneurysms: a causal event or a process running in parallel? The Tromsø study. Arterioscler Thromb Vasc Biol 2010;30:1263–8.

doi:10.1161/ATVBAHA.110.203588.

[10] Clark LT. Alcohol-induced hypertension: mechanisms, complications, and clinical implications. J Natl Med Assoc 1985;77:385–9.

[11] Kiechl S, Willeit J, Rungger G, Egger G, Oberhollenzer F, Bonora E. Alcohol consumption and atherosclerosis: What is the relation? : Prospective results from the Bruneck Study. Stroke 1998;29:900–7. doi:10.1161/01.STR.29.5.900.

[12] Ikehara S, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al. Alcohol consumption and mortality from stroke and coronary heart disease among Japanese men and women: the Japan collaborative cohort study. Stroke 2008;39:2936–42. doi:10.1161/STROKEAHA.108.520288.

[13] Tamakoshi A, Yoshimura T, Inaba Y, Ito Y, Watanabe Y, Fukuda K, et al. Profile of the JACC Study. J Epidemiol 2005;15:S4–8. doi:10.2188/jea.15.S4.

[14] Tamakoshi A, Ozasa K, Fujino Y, Suzuki K, Sakata K, Mori M, et al. Cohort profile of the Japan Collaborative Cohort Study at final follow-up. J Epidemiol 2013;23:227–32. doi:10.2188/jea.JE20120161.

[15] International guidelines for ethical review of epidemiological studies. Law Med Health Care 19:247–58.

[16] Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165:710–8. doi:10.1093/aje/kwk052.

[17] Toghill BJ, Saratzis A, Bown MJ. Abdominal aortic aneurysm—an independent disease to atherosclerosis? Cardiovasc Pathol 2017;27:71–5. doi:10.1016/j.carpath.2017.01.008.

[18] Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. BMJ 2011;342:d636.

doi:10.1136/bmj.d636.

[19] Takagi H, Yamamoto H, Iwata K, Goto S, Umemoto T, ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Effects of statin therapy on abdominal aortic aneurysm growth: A meta-analysis and meta-regression of observational comparative studies. Eur J Vasc Endovasc Surg 2012;44:287–92. doi:10.1016/j.ejvs.2012.06.021.

[20] Pai JK, Hankinson SE, Thadhani R, Rifai N, Pischon T, Rimm EB. Moderate alcohol consumption and lower levels of inflammatory markers in US men and women. Atherosclerosis 2006;186:113–20.

[21] Volpato S, Pahor M, Ferrucci L, Simonsick EM, Guralnik JM, Kritchevsky SB, et al. Relationship of alcohol intake with inflammatory markers and plasminogen activator inhibitior-1 in well-functioning older adults: The Health, Aging, and Body Composition Study. Circulation 2004;109:607–12. doi:10.1161/01.CIR.0000109503.13955.00.

[22] Harrison SC, Smith AJP, Jones GT, Swerdlow DI, Rampuri R, Bown MJ, et al. Interleukin-6 receptor pathways in abdominal aortic aneurysm. Eur Heart J 2013;34:3707–16. doi:10.1093/eurheartj/ehs354.

[23] Pikaar NA, Wedel M, van der Beek EJ, van Dokkum W, Kempen HJM, Kluft C, et al. Effects of moderate alcohol consumption on platelet aggregation, fibrinolysis, and blood lipids. Metabolism 1987;36:538–43. doi:10.1016/0026-0495(87)90163-6.

[24] Fiotti N, Tubaro F, Altamura N, Grassi G, Moretti M, Dapas B, et al. Alcohol reduces MMP-2 in humans and isolated smooth muscle cells. Alcohol 2008;42:389–95. doi:10.1016/j.alcohol.2008.02.001.

[25] Ridker PM. Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. JAMA 1994;272:929.

doi:10.1001/jama.1994.03520120039028.

[26] Longo GM, Xiong W, Greiner TC, Zhao Y, Fiotti N, Baxter BT. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. J Clin Invest 2002;110:625–32. doi:10.1172/JCI15334.

[27] Sakalihasan N, Delvenne P, Nusgens B V, Limet R, Lapière CM. Activated forms of MMP2 and MMP9 in abdominal aortic aneurysms. J Vasc Surg 1996;24:127–33. doi:10.1016/S0741-5214(96)70153-2.

[28] Wågsäter D, Vorkapic E, van Stijn CMW, Kim J, Lusis AJ, Eriksson P, et al. Elevated adiponectin levels suppress perivascular and aortic inflammation and prevent AngII-induced advanced abdominal aortic aneurysms. Sci Rep 2016;6:31414. doi:10.1038/srep31414.

[29] Martin LM, Leff M, Calonge N, Garrett C, Nelson DE. Validation of self-reported chronic conditions and health services in a managed care population. Am J Prev Med 2000;18:215–8. doi:10.1016/S0749-3797(99)00158-0.

[30] Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. Ann Thorac Surg 2002;73:17-27-8.

[31] Golledge J, Eagle KA. Acute aortic dissection. Lancet 2008;372:55–66. doi:10.1016/S0140-6736(08)60994-0.

[32] Geroldi D, Emanuele E. Moderate alcohol consumption and atherosclerosis: Friend or foe? Atherosclerosis 2010;210:367–8. doi:10.1016/j.atherosclerosis.2010.03.007.

[33] Schernthaner G-H, Herz C, Stangl H. Moderate alcohol consumption shifts to an atheroprotective phenotype: A glass of wine keeps atherosclerosis in check? Atherosclerosis 2016;254:305–6. doi:10.1016/j.atherosclerosis.2016.09.065.

Table 1. Age-adjusted mean values (standard errors) or prevalence of risk characteristics at baseline by alcohol consumption category for Japanese men.

			Ethanol intake, g per day		
	Never-drinkers	Ex-drinkers	≤30	>30	P for trend
Number of participants	7809	2374	12,151	12,386	
Age, years	59.0 (0.11)	62.4 (0.20)	56.7 (0.09)	55.4 (0.09)	0.003
Body mass index, kg/m^2	22.6 (0.03)	22.4 (0.06)	22.6 (0.03)	22.7 (0.03)	<0.0001
History of hypertension, %	14.0	24.0	19.6	23.9	<0.0001
History of diabetes mellitus, %	5.4	13.5	6.4	5.8	0.30
Current smoker, %	50.5	48.1	48.7	62.0	<0.0001

Table 2. Hazard ratios (HRs) of mortality from aortic diseases according to alcohol consumption categories among men.

			Ethanol intake, g per day		
	Never-drinkers	Ex-drinkers	≤30	>30	P for trend
Person-years	116,400	30,406	190,511	193,225	
Total aortic disease					
Number of cases	39	15	26	37	
Mortality rate, per 100,000 person-years	33.5	49.3	13.6	19.1	
Age-adjusted HR	1.00	1.31 (0.72–2.38)	0.51[a] (0.31–0.85)	0.87 (0.55–1.38)	0.90
Multivariable HR[b]	1.00	1.22 (0.66-2.23)	0.46[a] (0.28-0.76)	0.65 (0.41-1.04)	0.36
Aortic dissection					
Number of cases	14	8	4	19	
Mortality rate, per 100,000 person-years	12.0	26.3	2.1	9.8	
Age-adjusted HR	1.00	1.91 (0.80–4.56)	0.20[a] (0.06–0.59)	1.02 (0.51–2.06)	0.29
Multivariable HR[b]	1.00	1.62 (0.67-3.91)	0.16[a] (0.05-0.50)	0.70 (0.34-1.44)	0.84
Abdominal aortic aneurysm					
Number of cases	17	2	14	8	
Mortality rate, per 100,000 person-years	14.6	6.6	7.3	4.1	
Age-adjusted HR	1.00	0.39 (0.09–1.67)	0.64 (0.32–1.31)	0.47 (0.20–1.11)	0.15
Multivariable HR[b]	1.00	0.45 (0.10-1.96)	0.63 (0.31-1.30)	0.42[a] (0.18-1.00)	0.10

[a] $p < 0.05$
[b] Adjusted for age, body mass index, history of hypertension, history of diabetes mellitus, and smoking status.