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ORIGINAL RESEARCH

Risk Factors for Mortality From Aortic Aneurysm and Dissection: Results From a 26-Year Follow-Up of a Community-Based Population

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BACKGROUND: Aortic aneurysm rupture and acute aortic dissection are life-threatening conditions and represent an ever-growing public health challenge. Comprehensive epidemiologic investigations for their risk factors are scant. We aimed to investigate risk factors associated with mortality from aortic diseases through analysis of a community-based Japanese cohort.

METHODS AND RESULTS: IPHS (Ibaraki Prefectural Health Study) comprises 95 723 participants who took part in municipal health checkups in 1993. Factors considered for analysis included age, sex, body mass index, blood pressure, serum lipids (high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, and triglycerides), diabetes, antihypertensive and lipid-lowering drug use, and smoking and drinking habits. Cox proportional hazards models were applied to evaluate the associations between these variables and mortality from aortic diseases. During the median 26-year follow-up, 190 participants died of aortic aneurysm rupture, and 188 died of aortic dissection. An increased multivariable hazard ratio (HR) for mortality from total aortic diseases was observed for high systolic blood pressure (1.61 [1.00–2.59]), diastolic blood pressure (2.95 [1.95–4.48]), high non-HDL cholesterol (1.63 [1.19–2.24]), low HDL cholesterol (1.86 [1.29–2.68]), and heavy (>20 cigarettes/day) smoking habit (2.46 [1.66–3.63]). A lower multivariable HR was observed for diabetes (0.50 [0.28–0.89]).

CONCLUSIONS: Smoking habit, higher systolic blood pressure and diastolic blood pressure levels, higher non-HDL, and lower HDL cholesterol levels were positively associated with mortality from total aortic diseases, whereas diabetes was inversely associated.

Key Words: aortic diseases ■ cohort study ■ epidemiology ■ mortality ■ risk factor

Aortic aneurysm rupture and acute aortic dissection are life-threatening conditions and represent a major public health challenge. The term "aortic aneurysm" refers to a pathologic segment of aortic dilatation that has a propensity to expand and rupture. The dilatation of the aorta may occur as a result of atherosclerosis, aging, infection, inflammation, trauma, connective tissue disorders, medial degeneration, or a combination of these conditions.[1,2]

Abdominal aortic aneurysm is the most common form of aortic aneurysm with prevalence rates estimated at between 1.3% and 8.9% in men and between 1.0% and 2.2% in women.[2] Dilatation of the aorta, regardless of the section in which it occurs, is an

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CLINICAL PERSPECTIVE

What Is New?

- This population-based cohort study of Japanese residents provided evidence that smoking habit, high systolic and diastolic blood pressures, high non-high-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol levels were positively associated with mortality from total aortic diseases.
- Diabetes was inversely associated with that mortality.

What Are the Clinical Implications?

- The findings are expected to help guide cautious clinical management of patients with these risk factors, which partly overlap but not completely in accordance with those of other atherosclerotic cardiovascular diseases.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
SBP	systolic blood pressure

important precondition for rupture or dissection, and once ruptured/dissected, the overall mortality ranged from 65% to 90%.[3] The high fatality from such an event makes aortic disease an important cause, accounting for ≈10% of sudden deaths.[4,5]

In Japan, 19 126 people died of aortic diseases in 2017, accounting for ≈1.4% of all-cause mortality.[6] In the last couple of decades, the crude mortality from aortic disease among Japanese almost tripled, growing from 5.4 per 100 000 population in 1997 to 15.3 per 100 000 in population in 2017. That increase may mainly reflect population aging and partly reflect an increased number of diagnosed cases attributable to an improved medical transportation system and extended use of modern technology such as autopsy imaging for postmortem diagnosis.[7]

To date, the risk factors for aortic diseases have been vigorously sought. Previous studies have pointed out that smoking, hypertension, dyslipidemia, coronary heart disease, and family history of abdominal aortic aneurysm were likely to contribute to the development of abdominal aortic aneurysm.[2,8] In contrast, diabetes was reported to have an inverse association.[9] With regard to aortic dissection, underlying conditions leading to the fatal event seem to be highly diverse.[1]

However, no prospective study comprehensively examining the association of aortic diseases with a variety of risk factors has been conducted. Moreover, few studies have performed separate analyses for aortic aneurysm and aortic dissection within the same cohort with a large sample size and a long follow-up period. We aimed to investigate the risk factors for total aortic diseases, as well as for aortic aneurysm and dissection separately, through analysis of a community-based, Japanese cohort in Ibaraki prefecture followed up for >25 years, with a view to providing insights for future aortic disease management strategies.

METHODS

The data sets generated and analyzed during the current study are not publicly available owing to the restriction policy of the Ibaraki Prefectural Government, but they may be made available by the corresponding author upon reasonable request and with permission from the Ibaraki Prefectural Government.

Study Population

The study took place in Ibaraki Prefecture, which is located on Japan's Eastern Pacific coast, Northeast of Tokyo. With a population of ≈3 million, the prefecture has a highly developed industry profile and is a major producer of agricultural and manufactured products in Japan. The IPHS (Ibaraki Prefectural Health Study) cohort comprises 97 043 individuals (33 131 men and 63 912 women) aged between 40 and 79 years who participated in municipal health check-up services in 38 municipalities in Ibaraki prefecture in 1993. These 38 municipalities were selected out of a total of 85 in consideration of geographical balance and industry profiles to warrant representativeness. The size of the cohort is slightly <40% of the total prefectural population of the same age group. With regard to the age distribution of the cohort, individuals aged 40 to 49 years accounted for 22% of the cohort; 50 to 59 years for 24%; 60 to 69 years for 36%; and 70 to 79 years for 18%. A total of 95 723 individuals with complete health checkup data were eligible for analysis and were followed up until the end of 2019.

Baseline Examination

Factors considered for analysis included age, sex, body mass index, systolic and diastolic blood pressures, use of antihypertensive medication, serum lipid concentration (non-high-density lipoprotein [HDL] cholesterol, HDL cholesterol, and triglycerides), use of lipid-lowering medication, plasma glucose concentration, and smoking and alcohol consumption habits. The clinical characteristics were assessed, and the smoking and alcohol consumption habits were self-reported through face-to-face interviews at the initial health checkup.

End Points

The end point of this study was death from aortic diseases. It is believed that all deaths that occurred in the cohort were ascertained, unless the participants had moved from their original municipality during the follow-up period, in which case the follow-up of those participants was censored. The cause of death was determined on the basis of the official death certificate, classified as aortic dissection (I710) or aortic aneurysm (I711-I719) according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*). For each death that occurred during the follow-up between 1993 and 2019, the individual death form was obtained with the permission of the Ministry of Health, Labour and Welfare from the National Vital Statistics Survey and then matched with the municipal health checkup data.

Statistical Analysis

Age-adjusted least-square means of baseline characteristics and standard errors were calculated and compared between nondecedents and decedents of aortic aneurysm and dissection by use of the generalized linear regression models. From the baseline health checkup onwards, each participant was followed up until the earliest of the following: emigration from the original municipality, death, or the end of 2019. Cox proportional hazards models were applied to evaluate the association of each variable with mortality attributable to aortic diseases, and multivariable analysis was performed. The variables included in the model were age; sex; body mass index (<21, 21-<23, 23-<25, 25-<30, ≥30 kg/m^2); systolic blood pressure (SBP) (<120, 120–129, 130–139, 140–159, ≥160 mm Hg); diastolic blood pressure (DBP) (<80, 80–84, 85–89, 90–99, ≥100 mm Hg); antihypertensive medication use (dichotomous); non-HDL cholesterol (<130, 130–149, 150–169, ≥170 mg/dL); HDL cholesterol (<40, 40–49, 50–59, ≥60 mg/dL); triglycerides (<100, 100–149, 150–199, ≥200 mg/dL); lipid-lowering medication use (dichotomous); fasting status (<8 or ≥8 hours after a meal); plasma glucose level ("normal" defined as fasting plasma glucose <110 mg/dL or nonfasting plasma glucose <140 mg/dL; "impaired glucose tolerance" as fasting plasma glucose of 110–125 mg/dL or nonfasting plasma glucose of 140–199 mg/dL; and "diabetes" as fasting plasma glucose ≥126 mg/dL or nonfasting plasma glucose ≥200 mg/dL and/or use of antidiabetic medication); smoking status (never, former, or current smoker with 1–19 or ≥20 cigarettes/day); and alcohol consumption (never, former, or current drinker consuming <23, 23–45, 46–68, or ≥69 g/day). Since the SBP and DBP were highly correlated, we included the DBP, but not the SBP, in the main models. When SBP or DBP was examined as exposure, the counterpart of blood pressure was not adjusted. We tested proportional hazard, and we found no violation of proportionality.

The supplementary analyses were conducted for the combined category of SBP and DBP and for low-density lipoprotein (LDL) cholesterol as the exposure variable. Blood pressures were categorized into 4 groups taking account of both the SBP and the DBP on the basis of the 2017 American College of Cardiology/American Heart Association Guidelines, with hypertension stage 2 subdivided into 2 groups ("normal BP" defined as SBP <120 mm Hg and DBP <80 mm Hg; "elevated BP" as SBP 120–129 mm Hg and DBP <80 mm Hg; "hypertension stage 1" as SBP 130–139 mm Hg or DBP 80–89 mm Hg; "hypertension stage 2-1" as SBP 140–159 mm Hg or DBP 90–99 mm Hg; and "hypertension stage 2-2" as SBP ≥160 mm Hg or DBP ≥100 mm Hg). LDL cholesterol was calculated using the Friedewald formula: LDL cholesterol (mg/dL)=total cholesterol (mg/dL)–HDL cholesterol (mg/dL)–0.2×triglycerides (mg/dL) regardless of fasting status. People with triglyceride levels of ≥400 mg/dL were excluded from the analysis.

We estimated the probability of outcomes over time by using the cumulative incidence function to treat deaths from other than aortic diseases as a competing risk.[10]

All statistical tests were 2-sided, and probability values <0.05 were considered significant. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

Group informed consent to the conducting of an epidemiologic study was obtained from each of the municipalities, but individual consent was not required for this study since it was conducted as a secondary use of the data obtained for a public health practice on cardiovascular disease prevention in communities. In 1993, the baseline year of the study, the concept of informed consent was not widely spread in Japan, and thus individual consent was not obtained. Adhering to updated relevant guidelines and regulations afterwards, participants were retrospectively given the opportunity to withdraw their data from the analysis. Consent was considered to have been obtained if the individual had not explicitly declined participation in the study.

The IPHS protocol and use of data for epidemiologic studies were approved by the ethics committees of Ibaraki Prefecture and the University of Tsukuba.

RESULTS

Table 1 shows the participants' baseline characteristics at the time of enrollment. The cohort comprised 32 727 men and 62 996 women. Hypertension was a relatively common comorbidity, with approximately one fifth of the participants taking antihypertensive medication. Eight percent of the men and 4% of the women had

Table 1. Age-Adjusted Baseline Characteristics for Non-Cases and Deaths From Aortic Dissection and Aneurysm, Ibaraki Prefectural Health Study, 1993

	Men				Women			
	Non-cases (SEM)	Aortic dissection (SEM)	Aortic aneurysm (SEM)	*P* for overall difference	Non-cases (SEM)	Aortic dissection (SEM)	Aortic aneurysm (SEM)	*P* for overall difference
No.	32573	60	94		62772	128	96	
Age*, y	60.7	64.2	67.0	<0.001	58.1	64.1	66.5	<0.001
Body mass index, kg/m^2	23.3 (0.02)	23.5 (0.38)	23.6 (0.30)	0.09	23.6 (0.01)	24.1 (0.29)	24.4 (0.33)	0.08
Systolic blood pressure, mm Hg	136.6 (0.09)	137.0 (2.18)	142.6 (1.74)	0.17	132.1 (0.07)	138.9 (1.48)	140.3 (1.70)	0.03
Diastolic blood pressure, mm Hg	80.9 (0.06)	83.9 (1.39)	83.0 (1.11)	0.02	77.8 (0.04)	84.0 (0.93)	82.4 (1.07)	<0.001
Antihypertensive medication use, %	21.4	30.0	48.9	<0.001	20.8	34.4	36.5	0.09
Serum HDL cholesterol, mg/dL	52.4 (0.08)	48.1 (1.92)	47.9 (1.53)	<0.001	56.7 (0.06)	54.0 (1.23)	51.2 (1.42)	0.004
Serum non-HDL cholesterol, mg/dL	140.6 (0.19)	142.9 (4.53)	152.8 (3.62)	<0.001	151.0 (0.14)	158.0 (3.06)	169.6 (3.53)	0.003
Serum LDL cholesterol, mg/dL	111.6 (0.17)	111.2 (4.08)	125.3 (3.62)	<0.001	124.4 (0.12)	129.1 (2.76)	137.1 (3.21)	0.030
Serum triglycerides, mg/dL	117.5 (0.23)	111.0 (5.31)	115.1 (4.24)	0.17	108.6 (0.12)	107.3 (2.66)	111.5 (3.07)	0.17
Antidyslipidemic medication use, %	1.4	0	4.2	0.06	3.4	3.9	5.2	0.93
Diabetes, %	7.8	1.7	5.3	0.08	4.1	2.3	3.1	0.14
Current smoking, %	50.0	56.7	62.8	0.003	4.8	3.9	10.4	0.01
Current drinking, %	65.0	61.7	56.4	0.73	9.4	6.3	5.2	0.79

HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.
*Unadjusted.

diabetes. Smoking habit was more prevalent among the men than among the women; half of the men were smokers, whereas smokers accounted for only 5% of the women.

During a median of 26.0 years and a maximum of 26.7 years and >2 018 805 person-years of follow-up, 5287 participants (5.5%) emigrated from the cohort and 38 469 (40.2%) deaths occurred. One hundred ninety participants died of aortic aneurysm rupture (including 73 thoracic aneurysm cases and 84 abdominal aortic aneurysm cases), and 188 died of aortic dissection. As shown in Table 2 and the Figure, a higher multivariable hazard ratio (HR) of mortality from total aortic diseases was observed for high SBP (HR, 1.61 [1.00–2.59] for those with ≥160 mm Hg compared with <120 mm Hg), high DBP (HR, 2.95 [1.95–4.48] for those with ≥100 mm Hg compared with <80 mm Hg), high non-HDL cholesterol (HR, 1.63 [1.19–2.24] for those with non-HDL cholesterol ≥170 mg/dL compared with <130 mg/dL), low HDL cholesterol (HR, 1.86 [1.29–2.68] for those with HDL cholesterol <40 mg/dL compared with ≥60 mg/dL), and smoking habit (HR, 2.46 [1.66–3.63] among those who were current smokers with ≥20 cigarettes/day smoked compared with never smokers). On the other hand, lower HR of aortic disease mortality was observed for diabetes (HR, 0.50 [0.28–0.89]). Sex, body mass index, triglyceride concentration level, and alcohol consumption habit did not appear to be associated with mortality from aortic diseases. The values of 95% were not altered when bootstrap method was used (data not shown). The exclusion of cases in which death occurred within 5, 10, or 15 years of baseline did not alter the results materially (data not shown). The competing risk analysis did not alter the results materially (Table S1). For reference, the results of the univariate analysis are shown in Table S2. In the independent analyses for aortic dissection and for aortic aneurysm, the overall risk profiles proved generally similar except for a major difference identified in relation to serum cholesterol level: non-HDL cholesterol ≥170 mg/dL and HDL cholesterol <40 mg/dL were associated with 2.18 (1.40–3.41) times and 2.34 (1.40–3.92) times higher risk of mortality from aortic aneurysm, respectively, whereas no significant association was observed for serum non-HDL or HDL cholesterol level with aortic dissection mortality. It was also noted that the impact of high DBP on increasing mortality seemed to be greater for aortic dissection (ie, the HRs of mortality from aortic dissection for those with DBP 90–99 mm Hg and with DBP ≥100 mm Hg, compared with those with DBP <80 mm Hg, were 2.45 [1.62–3.69] and 5.16 [3.05–8.75]. The respective HRs of mortality from aortic aneurysm were 1.77 [1.18–2.64] and 1.47 [0.72–3.02]).

Notwithstanding the limited number of cases, we further classified aortic aneurysm into abdominal and thoracic aneurysms as a supplementary analysis (Table S3). The HRs for the variables examined were similar overall for thoracic and abdominal aortic aneurysms, but a major difference was observed for dyslipidemia: high non-HDL cholesterol levels, ie, ≥170 mg/dL compared with <130 mg/dL, were associated with a higher risk of mortality from abdominal aortic aneurysm (HR, 4.34 [2.17–8.64]), while no association was observed for thoracic aortic aneurysm (HR, 0.94 [0.46–1.91]).

As shown in the supplemental tables, a higher multivariable HR of mortality from total aortic diseases was observed, with 1.93 (1.21–3.08) for those with either SBP ≥160 mm Hg or DBP ≥100 mm Hg compared with those with SBP <120 mm Hg and DBP <80 mm Hg (Table S4) and with 1.59 (1.17–2.15) for those with LDL cholesterol ≥140 mg/dL compared with <100 mg/dL (Table S5).

DISCUSSION

Across more than 2 decades of follow-up of a community-based Japanese cohort, older age, smoking habit, higher SBP and DBP levels, higher non-HDL, and lower HDL cholesterol levels were positively associated with mortality from total aortic diseases, whereas diabetes was inversely associated.

Smoking was among the prominent risk factors. Current smokers of 1 to 19 cigarette(s)/day and of ≥20 cigarettes/day had higher mortality from aortic diseases, as compared with never smokers, by 1.9 and 2.5 times, respectively. This observation adds to a number of reports of previous studies that investigated the association between smoking and aortic diseases.[1,2,9,11–13] A meta-analysis of 23 prospective studies led to the summary that former and current smokers were at 2- to 5-times increased risk for abdominal aortic aneurysm. A dose–response relationship was also indicated,[14] consistent with our data. A previous report of another large community-based cohort study showed that passive smoking and current smoking were associated with excess mortality from aortic dissection and aneurysm (HR, 2.35 [1.09–5.09] for high passive smoking and 4.09 [1.99–8.39] for current smoking as compared with low passive smoking), with the effect stronger than that for coronary heart disease, which suggested the possibility that different pathophysiologic pathways exist between coronary heart diseases and aortic diseases.[15] Aneurysmal dilation and rupture result from the degradation of structural proteins of the extracellular matrix including medial elastin and adventitial collagen. The most prominent enzymes accelerating the degradation of these proteins are matrix metalloproteinases released by inflammatory cells.[16] Smoking may play a pivotal role in upregulating the production of metalloproteinases by activating relevant

Table 2. Number of Deaths and Multivariable Hazard Ratios (95% CIs) of Aortic Dissection and Aneurysm Among 95723 Japanese Men and Women: Ibaraki Prefectural Health Study 1993 to 2019

		No. of deaths and hazard ratios (95% CIs)								
	Total number	Aortic aneurysm			Aortic dissection			Combined		
Sex										
Men	32727	94	1.25	0.75–2.06	60	0.79	0.45–1.36	154	1.00	0.69–1.44
Women	62996	96	1.00		128	1.00		224	1.00	2.63–3.49
Age, 10 y			3.58	2.89–4.43		2.65	2.19–3.20		3.03	
Body mass index										
<21 kg/m^2	20078	35	1.19	0.75–1.88	37	1.36	0.86–2.15	72	1.26	0.91–1.75
21 to <23 kg/m^2	22567	35	0.87	0.56–1.36	42	1.16	0.75–1.79	77	1.01	0.74–1.37
23 to <25 kg/m^2	23267	46	1.00		41	1.00		87	1.00	
25 to <30 kg/m^2	25610	64	1.11	0.76–1.62	60	1.14	0.77–1.69	124	1.12	0.85–1.47
≥30 kg/m^2	2633	8	1.39	0.65–2.97	4	0.84	0.33–2.13	12	1.10	0.61–1.98
1 SD increase (3.15 kg/m^2)			1.02	0.87–1.20		0.97	0.83–1.14		1.00	0.89–1.11
Systolic blood pressure										
<120 mm Hg	43449	12	1.00		16	1.00		28	1.00	
120–129 mm Hg	25697	20	1.13	0.56–2.28	30	1.50	0.83–2.68	50	1.31	0.84–2.05
130–139 mm Hg	8403	46	1.64	0.88–3.06	46	1.56	0.89–2.71	92	1.57	1.04–2.37
140–159 mm Hg	14403	88	1.70	0.93–3.10	69	1.45	0.84–2.50	157	1.56	1.04–2.32
≥160 mm Hg	3725	22	1.42	0.70–2.90	23	1.89	0.99–3.60	45	1.61	1.00–2.59
1 SD increase (17.9 mm Hg)			1.15	0.99–1.35		1.11	0.95–1.30		1.13	1.01–1.26
Diastolic blood pressure										
<80 mm Hg	18229	57	1.00		50	1.00		107	1.00	
80–84 mm Hg	17324	50	1.21	0.83–1.77	49	1.44	0.97–2.13	99	1.31	1.00–1.72
85–89 mm Hg	21749	27	1.89	1.19–3.01	20	1.84	1.09–3.09	47	1.87	1.33–2.65
90–99 mm Hg	30188	45	1.77	1.18–2.64	45	2.45	1.62–3.69	90	2.06	1.54–2.74
≥100 mm Hg	8137	9	1.47	0.72–3.02	20	5.16	3.05–8.75	29	2.95	1.95–4.48
1 SD increase (10.7 mm Hg)			1.29	1.11–1.50		1.61	1.39–1.87		1.43	1.29–1.59
Antihypertensive medication	19813	81	1.74	1.28–2.37	61	1.26	0.91–1.74	142	1.49	1.20–1.87
Serum HDL cholesterol										
<40 mg/dL	10989	38	2.34	1.40–3.92	26	1.45	0.85–2.48	64	1.86	1.29–2.68
40 to <50 mg/dL	23852	69	2.04	1.32–3.15	57	1.48	0.98–2.23	126	1.73	1.28–2.32
50 to <60 mg/dL	26518	45	1.34	0.86–2.09	50	1.19	0.80–1.77	95	1.25	0.92–1.68
≥60 mg/dL	32796	36	1.00		51	1.00		87	1.00	
1 SD increase (14.5 mg/dL)			0.71	0.58–0.86		0.79	0.66–0.96		0.75	0.66–0.86
Serum non-HDL cholesterol										
<130 mg/dL	30998	37	1.00		35	1.00		72	1.00	
130 to <150 mg/dL	21239	26	1.03	0.63–1.66	33	1.18	0.77–1.82	59	1.11	0.81–1.53
150 to <170 mg/dL	18961	36	1.59	1.00–2.51	33	1.32	0.85–2.05	69	1.44	1.05–1.98
≥170 mg/dL	24479	64	2.18	1.40–3.41	45	1.20	0.77–1.89	109	1.63	1.19–2.24
1 SD increase (35.8 mg/dL)			1.44	1.23–1.68		1.05	0.89–1.24		1.24	1.10–1.39
Serum triglycerides										
<100 mg/dL	35380	48	1.00		63	1.00		111	1.00	
100 to <150 mg/dL	28307	63	1.01	0.67–1.50	57	0.80	0.56–1.20	120	0.90	0.69–1.19
150 to <200 mg/dL	15622	40	0.90	0.56–1.43	26	0.60	0.36–0.98	66	0.74	0.53–1.03
≥200 mg/dL	14846	37	0.68	0.41–1.13	38	0.86	0.53–1.39	75	0.74	0.52–1.06
1 SD increase (0.52 mg/dL)[†]			0.84	0.69–1.01		0.93	0.77–1.13		0.88	0.77–1.01
Lipid-lowering medication	2517	9	1.21	0.61–2.39	5	0.72	0.30–1.77	14	0.97	0.56–1.66

(*Continued*)

Table 2. Continued

		No. of deaths and hazard ratios (95% CIs)								
	Total number	Aortic aneurysm			Aortic dissection			Combined		
Serum glucose‡										
Normal	79275	160	1.00		169	1.00		329	1.00	
IGT	9932	21	0.83	0.52–1.31	12	0.56	0.32–0.99	33	0.70	0.49–0.99
Diabetes	4948	7	0.60	0.29–1.23	3	0.38	0.14–1.02	10	0.50	0.28–0.89
Smoking										
Never smoker	65928	98	1.00		133	1.00		231	1.00	
Former smoker	9305	21	1.10	0.60–2.02	14	0.89	0.44–1.80	35	0.98	0.62–1.55
Current smoker, 1–19 cigarette(s)/d	6855	32	3.07	1.86–5.08	7	0.68	0.30–1.55	39	1.85	1.23–2.77
Current smoker, ≥20 cigarettes/d	12067	37	2.68	1.56–4.59	30	2.40	1.34–4.28	67	2.46	1.66–3.63
Alcohol consumption										
Never drinker	65535	120	1.00		136	1.00		256	1.00	
Former drinker	2079	10	1.46	0.72–2.95	4	0.99	0.34–2.83	14	1.29	0.72–2.30
Current drinker, 1–22 g/d	7844	9	0.58	0.29–1.18	14	1.04	0.58–1.86	23	0.79	0.51–1.24
Current drinker, 23–45 g/d	9448	23	0.99	0.59–1.66	16	0.85	0.47–1.54	39	0.92	0.62–1.36
Current drinker, 46–68 g/d	7047	19	1.08	0.61–1.93	11	0.72	0.35–1.49	30	0.90	0.57–1.41
Current drinker, ≥69 g/d	2210	7	1.75	0.75–4.06	3	0.87	0.30–2.57	10	1.29	0.66–2.50

HDL indicates high-density lipoprotein; and IGT, impaired glucose tolerance.

Cox proportional hazards models included each covariate and fasting status. For the analysis of systolic blood pressure, diastolic blood pressure was not adjusted and vice versa.

†Log-transformed.

‡Normal: fasting glucose <110 mg/dL or nonfasting glucose <140 mg/dL; impaired glucose tolerance: fasting glucose 110–125 mg/dL or nonfasting glucose 140–199 mg/dL; diabetes: fasting glucose ≥126 mg/dL or nonfasting glucose ≥200 mg/dL and/or under diabetes treatment.

enzymes such as tissue plasminogen activator,[17] which accelerates proteolysis of the aortic matrix.

The association between blood pressure and aortic diseases has also been repeatedly pointed out.[1,2,11,18–20] In the present study, hypertension with either SBP≥140 mm Hg and/or DBP≥90 mm Hg, defined according to the 2017 American College of Cardiology/American Heart Association Guidelines, was associated with increased mortality from aortic diseases. Closer observation revealed that prominently increased mortality was observed among individuals with high DBP rather than among those with high SBP. A number of studies reported that DBP had a greater impact than SBP on the risk of abdominal aortic aneurysm, including a meta-analysis of 13 prospective studies concluding that the risk for abdominal aortic aneurysm increased by 14% for every 20-mm Hg increase in SBP (summary relative risk 1.14 [1.06–1.23]) and by 28% for every 10-mm Hg increase in DBP (summary relative risk 1.28 [1.12–1.46]).[21] Similarly, a high-resolution study based on a cohort of 1.25 million patients concluded that high SBP had a greater effect on angina and myocardial infarction than did DBP, whereas high DBP had a greater effect on abdominal aortic aneurysm (HR per 10-mm Hg increase, 1.45 [1.34–1.56]) than did SBP (HR per 20-mm Hg increase, 1.08 [1.00–1.17]).[22] These increments virtually agreed with the SDs in our study: 10.7 mm Hg for DBP and 17.9 mm Hg for SBP. The underlying mechanism by which diastolic hypertension enhances the risk of aortic diseases to a greater extent than does systolic hypertension is not well understood, but it was speculated that arterial stiffness represented by high SBP and low DBP might be protective against abdominal aortic aneurysm, accounting for the weak association with systolic hypertension and the stronger association with diastolic hypertension.[21,22] Although SBP may be a better predictor of risk for coronary heart disease[22] and stroke,[23] the current study indicated the importance of close monitoring of DBP for prevention of aortic disease deaths. The role of the renin-angiotensin system in the aneurysmal pathogenesis cannot be ignored. Previous studies suggested that the activation of angiotensin-1 receptors and the subsequent activation of transforming growth factor-β signaling promote extracellular matrix degradation, affecting the vascular integrity.[24,25]

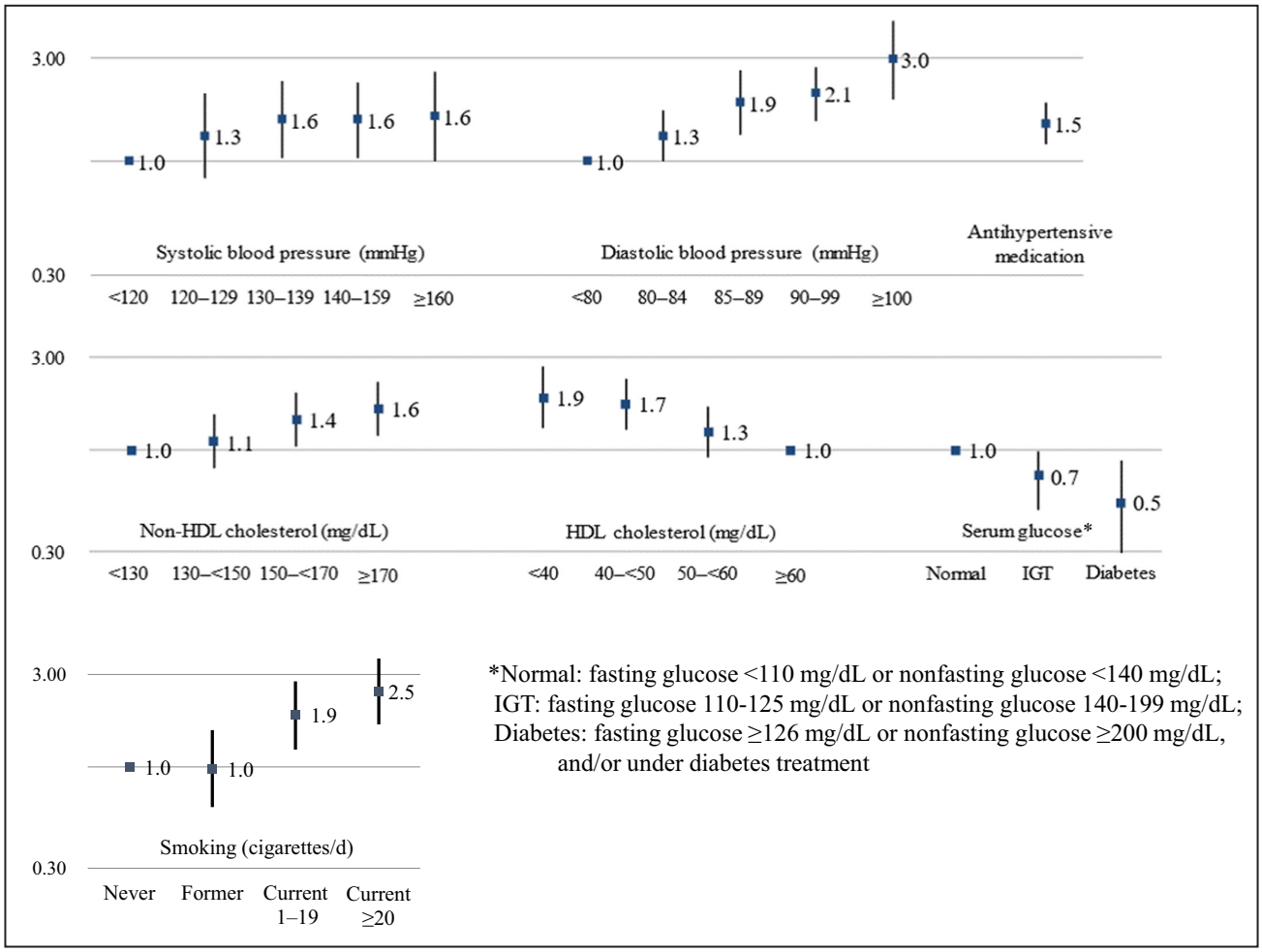

Figure. Multivariable hazard ratios (95% CIs) of mortality from aortic dissection and aneurysm.
HDL indicates high-density lipoprotein; and IGT, impaired glucose tolerance.

In the present study, low HDL cholesterol and high non-HDL cholesterol were associated with mortality from aortic aneurysm, but not from aortic dissection. The overall association with aortic disease mortality was similar between LDL cholesterol and non-HDL cholesterol (Table S3). Most previous studies were in agreement with the association between dyslipidemia and abdominal aortic aneurysm.[1,2,12,26] The current study revealed that high non-HDL cholesterol levels, ie, ≥170 mg/dL as compared with <130 mg/dL, were associated with a higher risk of mortality from abdominal aortic aneurysm (HR, 4.34 [2.17–8.64]), while no association was observed for thoracic aortic aneurysm (HR, 0.94 [0.46–1.91]) (Table S1). These findings may indicate that atherosclerosis plays a greater role in the pathogenesis of abdominal aortic aneurysm than in that of thoracic aortic aneurysm, as shown in previous studies.[27–29] A study comparing patients with ascending aortic aneurysm with controls showed less arterial calcification evaluated by computed tomography in the patients than in the controls.[27] Another study comparing the prevalence of coronary heart diseases and myocardial infarction in patients with a history of thoracic aortic aneurysm with that in controls identified a lower prevalence of coronary heart disease and myocardial infarction in the patients than in the controls.[28] As for a biologic mechanism of thoracic aortic aneurysm, an excess proteolytic balance of matrix metalloproteinase activity, with transforming growth factor-β modulating the extracellular matrix, is likely to lead to fragmentation of the elastic lamellae and disordered collagen deposition, which protects against plaque formation.[29]

A growing body of evidence suggests diabetes as a protective factor against aortic aneurysm.[2,8,11,12,21,26] Consistent with the findings of the current study, a number of preceding studies reported an inverse association between diabetes and prevalence and development of abdominal aortic aneurysm,[9,11,26,30] including a meta-analysis of 9 studies on the effect of diabetes on abdominal aortic aneurysm rupture that concluded that diabetes was inversely associated (HR,

0.71 [0.56–0.89]).[31] The mechanism underlying this finding is not clearly understood, but possible explanations include the following: (1) Diabetes may promote synthesis of and reduction in the degradation of the extracellular matrix through reduced expression of matrix metalloproteinases[32] and an increase in advanced glycation end products in the extracellular matrix, which help thicken the aortic wall. (2) Diabetic drugs such as thiazolidinediones and metformin may have a protective effect against abdominal aortic aneurysm through decreasing the expression of matrix metalloproteinases in the aortic wall.[9,33]

The risk factors for aortic dissection have been less understood, but hypertension and certain connective tissue diseases are thought to be the most common risk factors.[1,18] To the best of our knowledge, the current study is the first to elucidate a variety of risk or protective factors against aortic diseases, including separate analyses for aortic aneurysm and for aortic dissection within the same cohort. A large-scale community-based cohort of >90 000 men and women with a follow-up period of over 25 years made it possible not only to reinforce some of the findings of previous studies but also to introduce some novel findings. The current study identified less commonly observed risk/protective factors(ie, low HDL cholesterol and high non-HDL cholesterol levels) as being risk factors primarily for aortic aneurysm.

Some limitations of the present study deserve attention. First, low death rates from aortic diseases compared with from coronary heart diseases led to a small number of cases. We may have missed some risk or protective factors owing to lack of power to confirm the association with statistical significance. Second, we may have failed to capture some cases of aortic diseases, especially those of patients who died before hospital arrival.[7] However, it is unlikely that the identified cases had misdiagnosed aortic diseases, suggesting that our results were not undermined. Third, the measurement was taken only once at baseline and the analysis did not consider the changes in potential risk factors over time during the follow-up. Fourth, the lifestyle-related information we had was limited to smoking and alcohol consumption. With additional information such as diet and exercise, more in-depth analysis may be possible to elucidate which lifestyle behaviors would mitigate the risk of mortality from aortic diseases. Fifth, because of the study's observational design, we could not determine the causality between the factors and the outcome because of residual or unmeasured confounding.

In conclusion, we found that smoking habit, high SBP and DBP, high non-HDL cholesterol, and low HDL cholesterol were positively associated and diabetes was inversely associated with mortality from total aortic diseases. These results related to risk factors were similarly observed between aortic aneurysm and aortic dissection, but the association with non-HDL and HDL cholesterol levels was confined to aortic aneurysm, suggestive of a complex pathogenesis of aortic diseases, partly overlapping but not completely accordant with that of other atherosclerotic cardiovascular diseases.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Tables S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Number of deaths and multivariable hazard ratios (95% CIs) of aortic dissection and aneurysm among 95,723 Japanese men and women, adjusted for competing risks: Ibaraki Prefectural Health Study 1993-2019

	Total number	Number of deaths and hazard ratios (95% CIs)			
		Combined			
Sex					
Male	32,727	154	0.90	0.61 ,	1.33
Female	62,996	224	1.00		
Age, 10 years			**1.99**	**1.78 ,**	**2.22**
Body mass index					
<21 kg/m^2	20,078	72	1.13	0.80 ,	1.57
21-<23 kg/m^2	22,567	77	1.00	0.73 ,	1.35
23-<25 kg/m^2	23,267	87	1.00		
25-<30 kg/m^2	25,610	124	1.12	0.85 ,	1.47
≥30 kg/m^2	2,633	12	1.02	0.56 ,	1.84
1 SD increase (3.15 kg/m^2)			**1.11**	**1.00 ,**	**1.24**
Diastolic blood pressure					
<80 mmHg	18,229	107	1.00		
80-84 mmHg	17,324	99	**1.33**	**1.01 ,**	**1.75**
85-89 mmHg	21,749	47	**1.91**	**1.35 ,**	**2.71**
90-99 mmHg	30,188	90	**2.07**	**1.55 ,**	**2.77**
≥100 mmHg	8,137	29	**2.79**	**1.83 ,**	**4.25**
1 SD increase (10.7 mmHg)			**1.41**	**1.27 ,**	**1.56**
Antihypertensive medication	19,813	142	**1.38**	**1.10 ,**	**1.74**
Serum HDL cholesterol					
<40 mg/dl	10,989	64	**1.74**	**1.20 ,**	**2.53**
40-<50 mg/dl	23,852	126	**1.68**	**1.26 ,**	**2.24**
50-<60 mg/dl	26,518	95	1.23	0.91 ,	1.66
≥60 mg/dl	32,796	87	1.00		
1 SD increase (14.5 mg/dl)			**0.76**	**0.67 ,**	**0.88**
Serum non-HDL cholesterol					
<130 mg/dl	30,998	72	1.00		
130-<150 mg/dl	21,239	59	1.20	0.87 ,	1.65
150-<170 mg/dl	18,961	69	**1.58**	**1.14 ,**	**2.19**
≥170 mg/dl	24,479	109	**1.80**	**1.31 ,**	**2.47**
1 SD increase (35.8 mg/dl)			**1.27**	**1.14 ,**	**1.41**
Serum triglyceride					
<100 mg/dl	35,380	111	1.00		
100-<150 mg/dl	28,307	120	0.93	0.71 ,	1.22
150-<200 mg/dl	15,622	66	0.76	0.55 ,	1.06
≥200 mg/dl	14,846	75	0.78	0.56 ,	1.10
1 SD increase (0.52 mg/dl)†			0.90	0.79 ,	1.02
Lipid lowering medication	2,517	14	1.05	0.61 ,	1.81
Serum glucose‡					
Normal	79,275	329	1.00		
Impaired glucose tolerance	9,932	33	**0.67**	**0.47 ,**	**0.95**
Diabetes	4,948	10	**0.42**	**0.23 ,**	**0.75**
Smoking					
Never smoker	65,928	231	1.00		
Former smoker	9,305	35	0.94	0.58 ,	1.53
Current smoker, 1-19 cgrt(s)/day	6,855	39	**1.55**	**1.03 ,**	**2.33**
Current smoker, ≥20 cgrts/day	12,067	67	**2.00**	**1.31 ,**	**3.05**
Alcohol consumption					
Never drinker	65,535	256	1.00		
Former drinker	2,079	14	1.13	0.62 ,	2.04
Current drinker, 1-22 g/day	7,844	23	0.81	0.51 ,	1.27
Current drinker, 23-45 g/day	9,448	39	0.92	0.62 ,	1.36
Current drinker, 46-68 g/day	7,047	30	0.92	0.59 ,	1.46
Current drinker, ≥69g/day	2,210	10	1.25	0.64 ,	2.46

*Cox proportional hazard models included each covariate and fasting status.

†Log-transformed

‡Normal: fasting glucose <110 mg/dl or nonfasting glucose <140 mg/dl; impaired glucose tolerance: fasting glucose 110-125 mg/dl or nonfasting glucose 140-199 mg/dl; diabetes: fasting glucose ≥126 mg/dl or nonfasting glucose ≥200 mg/dl and/or under DM treatment

SD: standard deviation

Table S2. Number of deaths and univarite hazard ratios (95% CIs) of aortic dissection and aneurysm among 95,723 Japanese men and women: Ibaraki Prefectural Health Study 1993-2019

	Total number	Number of deaths and hazard ratios (95% CIs)											
		Aortic aneurysm				Aortic dissection				Combined			
Sex													
Male	32,727	94	**2.25**	**1.69 , 2.99**		60	1.10	0.81 , 1.50		154	**1.60**	**1.30 , 1.96**	
Female	62,996	96	1.00			128	1.00			224	1.00		
Age, 10 years			**3.75**	**3.08 , 4.57**			**2.58**	**2.16 , 3.07**			**3.08**	**2.70 , 3.51**	
Body mass index													
<21 kg/m^2	20,078	35	0.97	0.63 , 1.50		37	1.16	0.75 , 1.80		72	1.06	0.78 , 1.45	
21-<23 kg/m^2	22,567	35	0.79	0.51 , 1.22		42	1.05	0.69 , 1.62		77	0.91	0.67 , 1.24	
23-<25 kg/m^2	23,267	46	1.00			41	1.00			87	1.00		
25-<30 kg/m^2	25,610	64	1.24	0.85 , 1.81		60	1.33	0.90 , 1.97		124	1.28	0.98 , 1.68	
≥30 kg/m^2	2,633	8	1.52	0.72 , 3.21		4	1.07	0.42 , 2.70		12	1.30	0.73 , 2.33	
1 SD increase (3.15 kg/m^2)			1.14	0.99 , 1.31			1.09	0.94 , 1.26			**1.12**	**1.01 , 1.23**	
Systolic blood pressure													
<120 mmHg	43,449	12	1.00			16	1.00			28	1.00		
120-129 mmHg	25,697	20	1.67	0.83 , 3.36		30	**1.89**	**1.06 , 3.37**		50	**1.80**	**1.15 , 2.81**	
130-139 mmHg	8,403	46	**3.23**	**1.74 , 5.97**		46	**2.37**	**1.38 , 4.09**		92	**2.73**	**1.82 , 4.10**	
140-159 mmHg	14,403	88	**4.90**	**2.74 , 8.77**		69	**2.84**	**1.69 , 4.77**		157	**3.71**	**2.52 , 5.45**	
≥160 mmHg	3,725	22	**4.97**	**2.50 , 9.87**		23	**4.12**	**2.23 , 7.59**		45	**4.47**	**2.83 , 7.05**	
1 SD increase (17.9 mmHg)			**1.62**	**1.43 , 1.85**			**1.41**	**1.23 , 1.62**			**1.52**	**1.38 , 1.67**	
Diastolic blood pressure													
<80 mmHg	18,229	57	1.00			50	1.00			107	1.00		
80-84 mmHg	17,324	50	**1.53**	**1.05 , 2.23**		49	**1.62**	**1.10 , 2.39**		99	**1.57**	**1.20 , 2.06**	
85-89 mmHg	21,749	27	**2.49**	**1.58 , 3.93**		20	**2.03**	**1.21 , 3.40**		47	**2.27**	**1.62 , 3.19**	
90-99 mmHg	30,188	45	**2.44**	**1.66 , 3.61**		45	**2.70**	**1.82 , 4.02**		90	**2.57**	**1.94 , 3.39**	
≥100 mmHg	8,137	9	1.94	0.96 , 3.02		20	**5.01**	**3.02 , 8.30**		29	**3.40**	**2.27 , 5.09**	
1 SD increase (10.7 mmHg)			**1.43**	**1.25 , 1.64**			**1.60**	**1.40 , 1.83**			**1.52**	**1.38 , 1.67**	
Antihypertensive medication	19,813	81	**3.38**	**2.54 , 4.51**		61	**2.32**	**1.71 , 3.15**		142	**2.82**	**2.29 , 3.47**	
Serum HDL cholesterol													
<40 mg/dl	10,989	38	**3.30**	**2.11 , 5.18**		26	1.45	0.85 , 2.48		64	**2.34**	**1.71 , 3.22**	
40-<50 mg/dl	23,852	69	**2.63**	**1.76 , 3.94**		57	1.48	0.98 , 2.23		126	**2.03**	**1.54 , 2.66**	
50-<60 mg/dl	26,518	45	1.54	0.99 , 2.38		50	1.19	0.80 , 1.77		95	**1.35**	**1.01 , 1.80**	
≥60 mg/dl	32,796	36	1.00			51	1.00			87	1.00		
1 SD increase (14.5 mg/dl)			**0.61**	**0.52 , 0.72**			**0.77**	**0.66 , 0.90**			**0.69**	**0.61 , 0.77**	
Serum non-HDL cholesterol													
<130 mg/dl	30,998	37	1.00			35	1.00			72	1.00		
130-<150 mg/dl	21,239	26	1.10	0.69 , 1.75		33	1.32	0.87 , 2.01		59	1.22	0.89 , 1.66	
150-<170 mg/dl	18,961	36	**1.69**	**1.10 , 2.60**		33	**1.58**	**1.04 , 2.38**		69	**1.63**	**1.21 , 2.20**	
≥170 mg/dl	24,479	64	**2.33**	**1.59 , 3.41**		45	**1.53**	**1.03 , 2.26**		109	**1.90**	**1.45 , 2.50**	
1 SD increase (35.8 mg/dl)			**1.41**	**1.24 , 1.60**			**1.15**	**1.00 , 1.32**			**1.28**	**1.16 , 1.41**	
Serum triglyceride													
<100 mg/dl	35,380	48	1.00			63	1.00			111	1.00		
100-<150 mg/dl	28,307	63	**1.66**	**1.14 , 2.41**		57	1.15	0.80 , 1.65		120	**1.37**	**1.06 , 1.77**	
150-<200 mg/dl	15,622	40	**1.90**	**1.25 , 2.89**		26	0.95	0.60 , 1.50		66	**1.36**	**1.00 , 1.85**	
≥200 mg/dl	14,846	37	**1.75**	**1.15 , 2.67**		38	1.45	0.98 , 2.14		75	**1.58**	**1.19 , 2.11**	
1 SD increase (0.52 mg/dl)†			**1.24**	**1.08 , 1.43**			**1.15**	**1.00 , 1.32**			**1.19**	**1.08 , 1.32**	
Lipid lowering medication	2,517	9	1.78	0.91 , 3.48		5	0.99	0.41 , 2.41		14	1.39	0.82 , 2.37	
Serum glucose‡													
Normal	79,275	160	1.00			169	1.00			329	1.00		
Impaired glucose tolerance	9,932	21	1.12	0.71 , 1.77		12	0.66	0.38 , 1.17		33	0.89	0.62 , 1.26	
Diabetes	4,948	7	0.97	0.48 , 1.97		3	0.47	0.18 , 1.27		10	0.72	0.40 , 1.28	
Smoking													
Never smoker	65,928	98	1.00			133	1.00			231	1.00		
Former smoker	9,305	21	**1.77**	**1.11 , 2.83**		14	0.90	0.52 , 1.55		35	1.27	0.89 , 1.81	
Current smoker, 1-19 cgrt(s)/day	6,855	32	**3.95**	**2.65 , 5.89**		7	0.66	0.31 , 1.41		39	**2.08**	**1.48 , 2.92**	
Current smoker, ≥20 cgrts/day	12,067	37	**2.29**	**1.57 , 3.34**		30	**1.49**	**1.01 , 2.19**		67	**1.83**	**1.40 , 2.39**	
Alcohol consumption													
Never drinker	65,535	120	1.00			136	1.00			256	1.00		
Former drinker	2,079	10	**3.90**	**2.05 , 7.43**		4	1.43	0.53 , 3.87		14	**2.61**	**1.52 , 4.47**	
Current drinker, 1-22 g/day	7,844	9	0.61	0.31 , 1.20		14	0.83	0.48 , 1.44		23	0.73	0.48 , 1.12	
Current drinker, 23-45 g/day	9,448	23	1.44	0.93 , 2.26		16	0.89	0.53 , 1.50		39	1.15	0.82 , 1.61	
Current drinker, 46-68 g/day	7,047	19	1.58	0.98 , 2.57		11	0.82	0.44 , 1.51		30	1.18	0.81 , 1.72	
Current drinker, ≥69g/day	2,210	7	1.77	0.82 , 3.78		3	0.89	0.33 , 2.41		10	1.30	0.71 , 2.38	

†Log-transformed

‡Normal: fasting glucose <110 mg/dl or nonfasting glucose <140 mg/dl; impaired glucose tolerance: fasting glucose 110-125 mg/dl or nonfasting glucose 140-199 mg/dl; diabetes: fasting glucose ≥126 mg/dl or nonfasting glucose ≥200 mg/dl and/or under DM treatment

SD: standard deviation

Table S3. Number of deaths and multivariable hazard ratios (95% CIs) of aortic aneurysms according to serum cholesterol levels.

	Number of deaths and hazard ratios (95% CIs)								
	Thoracic aortic aneurysm (n=73)				Abdominal aortic aneurysm (n=84)				
Serum non-HDL cholesterol									
<130 mg/dl	20	1.00			15	1.00			
130-<150 mg/dl	16	0.99	0.50	1.96	9	0.91	0.39	2.11
150-<170 mg/dl	17	1.09	0.54	2.18	22	**2.80**	**1.39**	**5.63**
≥170 mg/dl	20	0.94	0.46	1.91	38	**4.34**	**2.17**	**8.64**
1 SD increase (35.8 mg/dl)		1.04	0.79	1.37		**1.83**	**1.46**	**2.28**
Serum HDL cholesterol									
<40 mg/dl	10	1.44	0.62	3.36	19	**3.11**	**1.38**	**7.00**
40-<50 mg/dl	29	1.88	1.00	3.57	29	**2.36**	**1.16**	**4.82**
50-<60 mg/dl	15	0.93	0.47	1.87	24	**2.03**	**1.00**	**4.12**
≥60 mg/dl	19	1.00			12	1.00		
1 SD increase (14.5 mg/dl)		0.85	0.64	1.13		**0.58**	**0.43**	**0.79**

* Adjusted for sex, age, BMI, diastolic blood pressure, antihypertensive medication, serum triglycerides, lipid lowering medication, DM, smoking habit and alcohol consumption
SD: standard deviation

Table S4. Number of deaths and multivariable hazard ratios (95% CIs) of aortic diseases according to systolic and diastolic blood pressures

	Number of deaths and hazard ratios (95% CIs)											
	Aortic aneurysm				Aortic dissection				Combined			
Blood pressure*												
Normal BP	12	1.00			13	1.00			25	1.00		
Elevated BP	13	0.99	0.46 ,	2.13	19	1.61	0.82 ,	3.17	32	1.29	0.78 ,	2.14
Hypertension stage 1	47	1.29	0.69 ,	2.40	49	1.56	0.87 ,	2.81	96	1.41	0.92 ,	2.17
Hypertension stage 2-1	91	1.51	0.83 ,	2.75	67	1.53	0.85 ,	2.74	158	**1.53**	**1.01 ,**	**2.32**
Hypertension stage 2-2	25	1.26	0.63 ,	2.53	36	**2.90**	**1.54 ,**	**5.47**	61	**1.93**	**1.21 ,**	**3.08**

* Blood pressure categorised according to ACC/AHA (2017), with modification ('stage 2 hypertension' divided into two categories)
Normal BP: SBP <120 mmHg and DBP <80 mmHg
Elevated BP: SBP 120-129 mmHg and DBP <80 mmHg
Hypertension stage 1: SBP 130-139 mmHg or DBP 80-89 mmHg
Hypertension stage 2-1: SBP 140-159 mmHg or DBP 90-99 mmHg
Hypertension stage 2-2: SBP≥ 160 mmHg or DBP≥ 100 mmHg

† Adjusted for sex, age, BMI, antihypertensive medication, serum HDL- C, serum non HDL-C, serum triglycerides, lipid lowering medication, DM, smoking habit and alcohol consumption

Table S5. Number of deaths and multivariable hazard ratios (95% CIs) of aortic diseases according to serum LDL and non-HDL cholesterol levels

	Number of deaths and hazard ratios (95% CIs)											
	Aortic aneurysm				Aortic dissection				Combined			
Serum LDL cholesterol												
<100 mg/dl	33	1.00			43	1.00			76	1.00		
100-<120 mg/dl	43	1.43	0.90 ,	2.26	52	1.19	0.79 ,	1.80	95	1.30	0.96 ,	1.77
120-<140 mg/dl	37	1.33	0.82 ,	2.16	39	0.90	0.58 ,	1.40	76	1.08	0.78 ,	1.50
≥140 mg/dl	75	**2.51**	**1.62 ,**	**3.88**	50	0.99	0.64 ,	1.52	125	**1.59**	**1.17 ,**	**2.15**
1 SD increase (31.9 mg/dl)		**1.41**	**1.22 ,**	**1.63**		1.03	0.88 ,	1.20		**1.21**	**1.09 ,**	**1.35**

* LDL cholesterol was calculated using the Friedewald formula, regardless of the fasting status, as follows:
LDL cholesterol (mg/dl) = total cholesterol (mg/dl) - HDL cholesterol (mg/dl) - 0.2*triglycerides (mg/dl)

†Adjusted for sex, age, BMI, diastolic blood pressure, antihypertensive medication, serum HDL- C, serum triglyceride, lipid lowering medication, DM, smoking habit and alcohol consumption

SD: standard deviation