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# Body Mass Index and Mortality From Aortic Aneurysm and Dissection

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**Aims:** Reports on an association between body mass index and aortic disease, which remains controversial. This study investigated the association between body mass index and mortality from aortic disease.

**Methods:** We conducted the Japan Collaborative Cohort Study, a prospective study of 103,972 Japanese men and women aged 40–79 years. Body mass index was calculated on the basis of self-reported height and weight, and the participants were followed up from 1988–89 through 2009. Sex-specific hazard ratios (95% confidence intervals) of mortality from aortic disease according to quintiles of body mass index were analyzed using the Cox proportional hazards model.

**Results:** During the median 18.8 years of follow-up, we documented 139 deaths due to aortic aneurysm (including 51 thoracic and 74 abdominal aortic aneurysms) and 134 deaths due to aortic dissection. We observed positive associations of body mass index with mortality from aortic aneurysm among men: the multivariable hazard ratios (95% confidence intervals) for highest versus lowest quintiles of body mass index were 4.48 (2.10–9.58), $P$ for trend $<0.0001$ for aortic aneurysm; 6.52 (1.33–32.02), $P=0.005$ for thoracic aortic aneurysm; 3.81 (1.39–10.49), $P=0.01$ for abdominal aortic aneurysm; and 2.71 (1.59–4.62), $P=0.001$ for total aortic disease. No association was found for aortic dissection. Among ever-smokers (men $\geq$ 90%) but not never-smokers (women $\geq$ 84%), an association between body mass index and aortic disease mortality was observed regardless of sex, which may explain the sex difference ($P$ for sex-interaction$=0.046$).

**Conclusions:** We found a positive association between body mass index and mortality from aortic aneurysm among Japanese men and smokers.

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**Key words:** Body mass index, Epidemiology, Vascular disease

## Introduction

Aortic disease, including aortic aneurysm and dissection, is a life-threatening disease with high fatality once rupture or complications occur[1, 2]. The mortality rate (per 100,000) from aortic disease increased from 5.3 in 1996 to 15.3 in 2017[3]. Many environmental and genetic risk factors contribute to the development of aortic disease[4, 5]. Obesity is one of the major risk factors for aortic disease and adverse outcomes after aneurysm repair surgery[6, 7].

Pathologically, the association between body mass index (BMI) and aortic disease may be explained by the degeneration of the aortic medial wall (the main pathogenic process of aortic disease) being partly caused by inflammation referred from the peripheral vascular adipose tissue (PVAT)[8, 9]. PVAT increases with an increasing BMI, an indicator of obesity[10]. This inflammation caused by PVAT may partly implicate an association between BMI and risk of aortic

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disease.

Results of epidemiologic prospective studies on the association between BMI and mortality from aortic disease were inconsistent. Two international database studies reported that a temporal trend in BMI was inversely associated with a temporal trend in age-standardized mortality from aortic disease[11, 12], whilst a prospective British study found no association[13]. However, studies on this issue considering various potential confounding factors were scant in Asian populations, whose BMI and prevalence of obesity are lower than those of Western populations[14].

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) Study is a nationwide, community-based follow-up study with one of the largest number of participants in Asia. We examined the associations of BMI with mortality from aortic disease in this cohort of men and women adjusted for various potential confounding factors. Our *a priori* hypothesis was that BMI would be associated with an increased risk of mortality from aortic disease in this population.

## Methods

### Study Cohort

The JACC Study comprised a nationwide community-based sample of 110,585 persons (46,395 men and 64,190 women) from 45 administrative districts of Japan. The prospective study participants were aged 40 to 79 years during the baseline period (1988–1990) and completed self-administered questionnaires concerning their lifestyles and medical histories of previous cardiovascular disease or cancer[15]. The following participants were excluded from the study: 6,613 participants for whom the self-reported height or weight was missing or inappropriate. As a result, 43,937 men and 60,035 women were included in the analysis. Written or explicitly verbal informed consent was obtained before the participants completed the questionnaire. In several communities, the informed consent was obtained from community leaders rather than from individual participants, which was the common practice for informed consent in Japan at that time. Individual informed consent was obtained in 36 of the 45 study areas; in the remaining 9 areas, group consent from the area leader was obtained. The JACC Study protocol was approved by the medical ethics committees of Hokkaido University, Osaka University, and the University of Tsukuba.

### Mortality Surveillance

In each community, the investigators conducted a systematic review of the death certificates. In Japan, registration of death is legally required and is believed to be followed across the country. Thus, all deaths that occurred in the cohort were ascertained by death certificates obtained from public health centers, except for participants who moved out of their original community during the follow-up (5.7%), in which case the participant was censored. The data on moving from the community were verified by population-register sheets. For each participant, the person-years of follow-up was conducted from the date the baseline questionnaire was filled out to the date of mortality from aortic disease, death from another cause, or moving out of the community or to the end of 2009, whichever occurred first; exceptions were made for areas in which the follow-up was ended earlier, i.e., 4 areas in 1999, 4 areas in 2003, and 2 areas in 2008. The median follow-up was 18.9 years. To identify mortality endpoints, we used the underlying cause of death coded by the International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD10): I711 to I712 for thoracic aortic aneurysm, I713 to I714 for abdominal aortic aneurysm, I715 to I716 for thoracoabdominal aortic aneurysm, I718 to I719 for aortic aneurysm of an unspecified site, I711 to I719 for total aortic aneurysm, I710 for aortic dissection, and I710 to I719 for total aortic disease.

### Measurements

The participants were asked to state their body weight (kg) and height ($m^2$) during the previous year in the baseline questionnaire. BMI was calculated as body weight divided by the square of height. Also, we asked various questions on lifestyle in the baseline questionnaire, including age, sex, smoking status, alcohol intake, perceived mental stress, walking, sports, fresh fish intake, employment status, education level (the age of the highest school attainment) and histories of hypertension, hyperlipidemia, and diabetes mellitus.

### Statistical Analysis

Age-adjusted means and proportions of selected cardiovascular risk factors were calculated according to quintiles of BMI, and the overall difference across the quintiles was tested by analysis of covariance. Sex-specific hazard ratios (HRs) with 95% confidence intervals (CIs) for each quintile compared with the lowest quintile were calculated after being stratified by area and with adjustments for age and other potential confounding factors using Cox proportional hazards survival models. Potential confounding factors included smoking status (never, former smoker, or current smoker of 1–19 or ≥ 20 cigarettes/day); alcohol intake (never, former drinker, or current drinker of ethanol at 1–22, 23–45, 46–68, or ≥ 69 g/day; 23 g ethanol corresponds to 1 *go*, a Japanese traditional unit of volume); perceived mental stress (low, medium, or high); walking (rarely, 30, 30–60, or >60 min/day); sports (rarely, 1–2, 3–4, or ≥ 5 h/week); education level (age of completed education of ≤ 18 or ≥ 19 years); fresh fish intake (almost never, 1–2 times/month, 1–2 times/week, 3–4 times/week, or almost every day); employment status (full-time worker, part-time worker, independent business, or full-time homemaker, unemployed, or others) in model 1. As the causal pathway, we added histories of hypertension, hyperlipidemia, and diabetes mellitus in the multivariable model (yes or no) (model 2). Indicator variables were used for missing variables. The linear trend of the HRs across the quintiles was tested by using variables with -2, -1, 0, 1, and 2 assigned to successive quintiles. Multiplicative interactions with male or female sex and smoking status of ever (current or former smoker) vs never smokers were tested using a cross-product term. Also, we conducted a sex-specific smoking-stratified analysis.

M.T. and K.Y. demonstrated full access to all of the data in the study, and they take responsibility for the integrity of the data and the accuracy of the data analysis. We used SAS version 9.4 (SAS Institute, Cary, NC, USA) for the analyses. All probability values for the statistical tests were 2-tailed, and values below 0.05 were regarded as significant.

## Results

During a median 18.8 years of follow-up for 103,972 persons (43,937 men and 60,035 women), we documented 139 deaths due to aortic aneurysm (51 thoracic aortic aneurysms, 74 abdominal aortic aneurysms, 7 thoracoabdominal aortic aneurysms, and 7 aortic aneurysm of unspecified site) and 134 deaths due to aortic dissection. Among women, 39 deaths occurred from aortic aneurysm (19 thoracic aortic aneurysms, 17 abdominal aortic aneurysms, and 3 aortic aneurysms of unspecified site) and 68 deaths from aortic dissection.

The baseline characteristics of the study cohort according to quintiles of BMI are shown in **Table 1**. Age, current smoking, perceived mental stress, walking, and unemployment were inversely correlated with BMI in both men and women. Current drinking, hypertension, and diabetes mellitus were positively correlated with BMI in both men and women. Exercise and education were correlated with BMI positively in men but inversely in women.

As shown in **Table 2**, BMI was positively associated with mortality from total aortic diseases and total aortic aneurysms among men. The associations were essentially the same for thoracic aortic aneurysms and abdominal aortic aneurysms. The multivariable HRs (95% CI) for each quintile compared with the lowest quintiles of BMI among men were 1.73 (1.02–2.92) in the second quintile, 1.90 (1.12–3.22) in the third, 1.90 (1.11–3.26) in the fourth, and 2.71 (1.59–4.62) in the highest quintile, *P* for trend = 0.001 for total aortic disease; 4.48 (2.10–9.58) in the highest quintile, *P* for trend < 0.0001 for total aortic aneurysm; 6.52 (1.33–32.02) in the highest quintile, *P* for trend = 0.005 for thoracic aortic aneurysm; and 3.81 (1.39–10.49) in the highest quintile, *P* for trend = 0.01 for abdominal aortic aneurysm. The respective HRs (95% CI) among women were 0.97 (0.53–1.78) in the second quintile, 0.90 (0.49–1.67) in the third, 0.83 (0.44–1.57) in the fourth, and 1.17 (0.66–2.04) in the highest quintile, *P* for trend = 0.82 for total aortic disease; 0.96 (0.42–2.19) in the highest quintile, *P* for trend = 0.47 for total aortic aneurysm; 1.56 (0.49–4.99) in the highest quintile, *P* for trend = 0.93 for thoracic aortic aneurysm; 0.58 (0.15–2.24) in the highest quintile, *P* for trend = 0.47 for abdominal aortic aneurysm. A significant interaction with BMI by sex was found in relation to total aortic aneurysm (*P* for interaction = 0.046). No associations were observed for aortic dissection in either men or women.

Similar results were observed when histories of hypertension, hyperlipidemia, and diabetes mellitus, as mediating factors between BMI and aortic disease, were adjusted for; for example, the multivariable HRs (95% CI) for the highest quintiles compared with the lowest quintiles of BMI were 2.26 (1.32–3.87), *P* for trend = 0.006 for total aortic disease among men, and 0.97 (0.55–1.72), *P* for trend = 0.68 among women **(Supplemental Table 1)**.

As for potential effect modification by smoking status, the association was more prominent for ever-smokers: the multivariable HRs (95% CI) was 2.63 (1.50–4.60) in the highest quintile, *P* for trend = 0.002 for total aortic disease; 4.04 (1.83–8.95) in the highest quintile, *P* for trend = 0.001 for total aortic aneurysm; 2.73 (1.03–7.21) in the highest quintile, *P* for trend = 0.05 for abdominal aortic aneurysm. As for never-smokers, the respective HRs (95% CI) were 1.15 (0.67–1.97), *P* for trend = 0.82 for total aortic disease; 1.10 (0.50–2.46), *P* for trend = 0.98 for total aortic aneurysm; 1.04 (0.26–4.12), *P* for trend = 0.94 for abdominal aortic aneurysm **(Table 3)**. The interaction was significant for total aortic aneurysm (*P* = 0.008), but not for the other outcomes (*P* for interaction = 0.099 for total aortic disease and 0.520 for abdominal aortic aneurysm).

**Table 1.** Age-adjusted baseline characteristics according to quintiles of body mass index, 43,937 men and 60,035 women, JACC Study

| | Body Mass Index (kg/m$^2$) | | | | | |
|---|---|---|---|---|---|---|
| | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | *P* for overall difference |
| Men, *n* | 8,908 | 9,390 | 8,998 | 8,959 | 7,682 | |
| Age at baseline, years | 60.4 | 57.8 | 57.0 | 56.1 | 55.4 | < 0.001 |
| Body mass index, kg/m$^2$ | 19.0 | 21.1 | 22.6 | 24.1 | 26.9 | < 0.001 |
| Current drinkers, % | 66.8 | 71.0 | 72.5 | 72.1 | 69.2 | < 0.001 |
| Current smokers, % | 62.6 | 57.1 | 52.1 | 47.8 | 45.0 | < 0.001 |
| Ex- smokers, % | 20.8 | 24.2 | 27.3 | 30.4 | 30.6 | < 0.001 |
| High perceived mental stress, % | 25.4 | 21.9 | 21.9 | 23.0 | 22.8 | < 0.001 |
| Walking ≥ 30 min/day, % | 87.8 | 88.8 | 88.7 | 86.7 | 84.7 | < 0.001 |
| Exercise ≥ 5 h/week, % | 7.3 | 7.4 | 7.3 | 6.9 | 7.4 | < 0.001 |
| College or higher education, % | 16.0 | 17.2 | 18.3 | 18.7 | 18.6 | < 0.001 |
| Fresh fish intake, times/week | 6.8 | 6.9 | 7.1 | 7.1 | 7.0 | < 0.001 |
| Unemployeed, % | 19.5 | 16.8 | 17.4 | 17.1 | 16.9 | < 0.001 |
| Hypertension, % | 14.6 | 18.4 | 21.2 | 25.0 | 30.0 | < 0.001 |
| Diabetes mellitus, % | 6.0 | 6.7 | 7.2 | 7.2 | 8.7 | < 0.001 |
| Hyperlipidemia, % | 0.1 | 0.1 | 0.2 | 0.3 | 0.2 | 0.23 |
| Women, *n* | 11,761 | 11,407 | 11,941 | 11,854 | 13,072 | |
| Age at baseline, years | 58.9 | 56.8 | 56.7 | 57.1 | 57.6 | < 0.001 |
| Body mass index, kg/m$^2$ | 18.8 | 21.1 | 22.6 | 24.2 | 27.3 | < 0.001 |
| Current drinkers, % | 14.3 | 14.9 | 15.1 | 15.7 | 14.8 | < 0.001 |
| Current smokers, % | 6.9 | 5.0 | 4.7 | 4.7 | 5.7 | < 0.001 |
| Ex- smokers, % | 1.7 | 1.6 | 1.3 | 1.6 | 2.1 | < 0.001 |
| High perceived mental stress, % | 22.2 | 20.5 | 19.9 | 19.5 | 19.6 | < 0.001 |
| Walking ≥ 30 min/day, % | 89.4 | 90.1 | 90.2 | 88.8 | 87.8 | < 0.001 |
| Exercise ≥ 5 h/week, % | 4.6 | 5.0 | 4.6 | 4.5 | 4.1 | < 0.001 |
| College or higher education, % | 11.8 | 10.7 | 11.1 | 9.0 | 8.1 | < 0.001 |
| Fresh fish intake, times/week | 6.9 | 6.9 | 7.2 | 7.2 | 7.2 | < 0.001 |
| Unemployeed, % | 22.0 | 20.7 | 20.0 | 19.5 | 20.5 | < 0.001 |
| Hypertension, % | 14.0 | 18.7 | 22.2 | 25.9 | 34.2 | < 0.001 |
| Diabetes mellitus, % | 3.3 | 3.8 | 4.4 | 4.0 | 5.5 | < 0.001 |
| Hyperlipidemia, % | 0.2 | 0.2 | 0.3 | 0.3 | 0.2 | 0.64 |

To seek the reasons for the sex difference, we further conducted sex-specific smoking-stratified analyses **(Table 4)**. We found similar positive trends between BMI and mortality from total aortic disease in smokers for both sexes: multivariable HRs (95% CI) in the highest quintile = 2.83 (1.54–5.17), *P* for trend = 0.002 among men, and 1.93 (0.31–12.07), *P* for trend = 0.53 among women. As for never-smokers, no associations were found between BMI and aortic disease, regardless of sex. These results underscore that the sex difference could be explained by the confounding of smoking.

## Discussion

In this large community-based prospective cohort study, we observed generally positive associations of BMI with mortality risk from thoracic aortic aneurysm, abdominal aortic aneurysm, and total aortic disease among men, whilst no association was observed among women. As for aortic dissection, BMI was not associated with mortality. This is the first report to find a positive association between BMI and aortic disease in an Asian population, which demonstrates a lower BMI than those of Western populations.

**Table 2.** Age- adjusted and area- stratified, and multivariable hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality from aortic aneurysm and aortic dissection, JACC study, 43,937 men and 60,035 women

| | Body Mass Index (kg/m$^2$) | | | | | |
|---|---|---|---|---|---|---|
| Men | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | Trend *P* |
| Person-years | 128,397 | 147,636 | 144,567 | 145,786 | 125,440 | |
| Total aortic disease (*n*) | 23 | 37 | 37 | 33 | 36 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 1.61 (0.95-2.71) | 1.74 (1.03-2.94) | 1.67 (0.97-2.85) | 2.30 (1.36-3.92) | 0.004 |
| Multivariable* HR (95%CI) | 1.0 | 1.73 (1.02-2.92) | 1.90 (1.12-3.22) | 1.90 (1.11-3.26) | 2.71 (1.59-4.62) | 0.001 |
| Total aortic aneurysm (*n*) | 10 | 22 | 21 | 25 | 22 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 2.34 (1.10-4.95) | 2.47 (1.16-5.28) | 3.22 (1.54-6.74) | 3.70 (1.74-7.87) | <.0001 |
| Multivariable* HR (95%CI) | 1.0 | 2.52 (1.18-5.35) | 2.75 (1.28-5.88) | 3.71 (1.77-7.80) | 4.48 (2.10-9.58) | <.0001 |
| Thoracic aortic aneurysm (*n*) | 2 | 5 | 8 | 10 | 7 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 2.75 (0.53-14.21) | 4.87 (1.03-23.13) | 6.42 (1.39-29.54) | 6.01 (1.23-29.35) | 0.010 |
| Multivariable* HR (95%CI) | 1.0 | 2.73 (0.52-14.24) | 5.55 (1.16-26.51) | 7.77 (1.67-36.06) | 6.52 (1.33-32.02) | 0.005 |
| Abdominal aortic aneurysm (*n*) | 6 | 15 | 12 | 13 | 11 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 2.61 (1.01-6.77) | 2.28 (0.85-6.10) | 2.77 (1.04-7.35) | 3.05 (1.12-8.34) | 0.04 |
| Multivariable* HR (95%CI) | 1.0 | 2.80 (1.08-7.29) | 2.49 (0.92-6.70) | 3.27 (1.23-8.72) | 3.81 (1.39-10.49) | 0.01 |
| Aortic dissection (*n*) | 13 | 15 | 16 | 8 | 14 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 1.06 (0.51-2.24) | 1.18 (0.57-2.47) | 0.61 (0.25-1.49) | 1.30 (0.60-2.81) | 0.98 |
| Multivariable* HR (95%CI) | 1.0 | 1.12 (0.53-2.36) | 1.26 (0.60-2.66) | 0.67 (0.27-1.63) | 1.48 (0.68-3.21) | 0.77 |
| Women | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | Trend *P* |
| Person-years | 185,234 | 190,096 | 199,846 | 197,440 | 217,566 | |
| Total aortic disease (*n*) | 23 | 20 | 19 | 17 | 28 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 0.98 (0.54-1.78) | 0.89 (0.49-1.65) | 0.81 (0.43-1.52) | 1.20 (0.68-2.10) | 0.80 |
| Multivariable* HR (95%CI) | 1.0 | 0.97 (0.53-1.78) | 0.90 (0.49-1.67) | 0.83 (0.44-1.57) | 1.17 (0.66-2.04) | 0.82 |
| Total aortic aneurysm (*n*) | 12 | 6 | 6 | 3 | 12 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 0.59 (0.22-1.57) | 0.58 (0.22-1.56) | 0.29 (0.08-1.05) | 1.05 (0.46-2.40) | 0.59 |
| Multivariable* HR (95%CI) | 1.0 | 0.59 (0.22-1.60) | 0.59 (0.22-1.61) | 0.29 (0.08-1.05) | 0.96 (0.42-2.19) | 0.47 |
| Thoracic aortic aneurysm (*n*) | 5 | 3 | 2 | 1 | 8 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 0.68 (0.16-2.87) | 0.44 (0.09-2.30) | 0.22 (0.03-1.91) | 1.61 (0.51-5.07) | 0.91 |
| Multivariable* HR (95%CI) | 1.0 | 0.64 (0.15-2.73) | 0.43 (0.08-2.28) | 0.23 (0.03-1.98) | 1.56 (0.49-4.99) | 0.93 |
| Abdominal aortic aneurysm (*n*) | 6 | 2 | 3 | 2 | 4 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 0.41 (0.08-2.02) | 0.63 (0.16-2.53) | 0.42 (0.08-2.11) | 0.75 (0.20-2.75) | 0.74 |
| Multivariable* HR (95%CI) | 1.0 | 0.43 (0.08-2.25) | 0.76 (0.18-3.24) | 0.37 (0.07-1.97) | 0.58 (0.15-2.24) | 0.47 |
| Aortic dissection (*n*) | 11 | 14 | 13 | 14 | 16 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 1.40 (0.63-3.09) | 1.24 (0.55-2.77) | 1.34 (0.61-2.98) | 1.39 (0.64-3.03) | 0.48 |
| Multivariable* HR (95%CI) | 1.0 | 1.40 (0.63-3.10) | 1.25 (0.56-2.80) | 1.39 (0.63-3.08) | 1.40 (0.64-3.05) | 0.45 |

*Adjustment for age, alcohol intake, cigarette smoking status, perceived mental stress, walking, sports, educational level, fresh fish intake, and employment status.

Previous reports on the association between BMI and mortality from aortic aneurysm were modest[11-13, 16]. Two previous studies using ecological regression analysis based on international databases (13 European, 2 Australian, 2 North American, and 1 Asian country) suggested that a temporal trend in BMI was inversely associated with a temporal trend in age-standardized mortality from thoracic aortic aneurysm[11] and abdominal aortic aneurysm[12]; however, they did not take into account any confounding factors. The other prospective study of 335,308 men and women aged 37 to 73 years by the UK Biobank found no association between BMI and mortality from aortic aneurysm (multivariable HR, 95% CI per unit increase in BMI = 1.03, 0.98–1.08), probably because of a large difference in the distribution of BMI (average BMI ± SD were 27.4 ± 4.7 kg/m$^2$ in the UK study and 22.8 ± 3.0 kg/m$^2$ in the present study)[13]. The other prospective cohort study of 63,655 men and women aged 46 to 84 years from the data of the Swedish Mammogra-

**Table 3.** Age- and sex- adjusted and area- stratified, and multivariable hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality from aortic aneurysm and aortic dissection, JACC study, 37,286 ever smokers and 66,686 never smokers

| | Body Mass Index (kg/m$^2$) | | | | | | |
|---|---|---|---|---|---|---|---|
| Ever smokers | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | Trend *P* | *P* for interaction |
| Person-years | 114,622 | 125,117 | 118,882 | 118,161 | 104,307 | | |
| Total aortic disease (*n*) | 20 | 38 | 34 | 33 | 35 | | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 1.98 (1.15-3.42) | 2.00 (1.15-3.50) | 2.07 (1.18-3.63) | 2.69 (1.54-4.70) | 0.001 | |
| Multivariable* HR (95%CI) | 1.0 | 2.04 (1.18-3.51) | 1.96 (1.12-3.43) | 2.04 (1.17-3.58) | 2.63 (1.50-4.60) | 0.002 | 0.099 |
| Total aortic aneurysm (*n*) | 9 | 23 | 19 | 24 | 21 | | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 2.85 (1.32-6.19) | 2.74 (1.24-6.10) | 3.74 (1.73-8.09) | 4.10 (1.86-9.04) | < .0001 | |
| Multivariable* HR (95%CI) | 1.0 | 2.93 (1.35-6.36) | 2.64 (1.18-5.88) | 3.63 (1.68-7.86) | 4.04 (1.83-8.95) | 0.001 | 0.008 |
| Thoracic aortic aneurysm (*n*) § | 1 | 7 | 6 | 10 | 6 | | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | - | - | - | - | - | - | |
| Multivariable* HR (95%CI) | - | - | - | - | - | - | - |
| Abdominal aortic aneurysm (*n*) | 7 | 14 | 12 | 12 | 11 | | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 2.19 (0.88-5.45) | 2.16 (0.85-5.54) | 2.42 (0.94-6.20) | 2.70 (1.03-7.09) | 0.05 | |
| Multivariable* HR (95%CI) | 1.0 | 2.23 (0.89-5.57) | 2.06 (0.80-5.31) | 2.38 (0.93-6.12) | 2.73 (1.03-7.21) | 0.05 | 0.520 |
| Aortic dissection (*n*) | 11 | 15 | 15 | 9 | 14 | | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 1.31 (0.60-2.85) | 1.41 (0.64-3.09) | 0.88 (0.36-2.13) | 1.61 (0.72-3.60) | 0.55 | |
| Multivariable* HR (95%CI) | 1.0 | 1.35 (0.62-2.95) | 1.40 (0.64-3.07) | 0.87 (0.36-2.13) | 1.55 (0.69-3.46) | 0.64 | 0.920 |

| Never smokers | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | Trend *P* |
|---|---|---|---|---|---|---|
| Person-years | 199,010 | 212,615 | 225,531 | 225,064 | 238,699 | |
| Total aortic disease (*n*) | 26 | 19 | 22 | 17 | 29 | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 0.80 (0.44-1.45) | 0.90 (0.51-1.59) | 0.71 (0.38-1.31) | 1.17 (0.68-2.00) | 0.77 |
| Multivariable* HR (95%CI) | 1.0 | 0.82 (0.45-1.48) | 0.91 (0.51-1.61) | 0.72 (0.39-1.33) | 1.15 (0.67-1.97) | 0.82 |
| Total aortic aneurysm (*n*) | 13 | 5 | 8 | 4 | 13 | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 0.43 (0.15-1.22) | 0.70 (0.29-1.69) | 0.36 (0.12-1.12) | 1.17 (0.53-2.57) | 0.91 |
| Multivariable* HR (95%CI) | 1.0 | 0.46 (0.16-1.29) | 0.71 (0.29-1.74) | 0.36 (0.12-1.13) | 1.10 (0.50-2.46) | 0.98 |
| Thoracic aortic aneurysm (*n*) | 6 | 1 | 4 | 1 | 9 | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 0.19 (0.02-1.59) | 0.75 (0.21-2.69) | 0.19 (0.02-1.58) | 1.66 (0.57-4.83) | 0.58 |
| Multivariable* HR (95%CI) | 1.0 | 0.18 (0.02-1.53) | 0.77 (0.21-2.78) | 0.19 (0.02-1.59) | 1.66 (0.56-4.94) | 0.56 |
| Abdominal aortic aneurysm (*n*) | 5 | 3 | 3 | 3 | 4 | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 0.68 (0.16-2.86) | 0.70 (0.16-2.95) | 0.76 (0.18-3.22) | 1.05 (0.28-4.02) | 0.90 |
| Multivariable* HR (95%CI) | 1.0 | 0.82 (0.19-3.52) | 0.82 (0.19-3.59) | 0.85 (0.19-3.78) | 1.04 (0.26-4.12) | 0.94 |
| Aortic dissection (*n*) | 13 | 14 | 14 | 13 | 16 | |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0 | 1.16 (0.55-2.48) | 1.11 (0.52-2.37) | 1.05 (0.49-2.28) | 1.22 (0.58-2.56) | 0.73 |
| Multivariable* HR (95%CI) | 1.0 | 1.20 (0.56-2.57) | 1.12 (0.53-2.40) | 1.08 (0.50-2.35) | 1.25 (0.60-2.62) | 0.69 |

*Adjustment for age, sex, alcohol intake, perceived mental stress, walking, sports, educational level, fresh fish intake, and employment status.
§The results for thoracic aortic aneurysm were not presented due to small number of cases.

phy Cohort and the aforementioned Cohort of Swedish Men combined, with a mean of 12.0 years of follow-up, found no association between BMI and abdominal aortic aneurysm, probably because of a difference in the exclusion criteria (individuals with BMI < 17.9 kg/m$^2$ were excluded from the study) and assessment of abdominal aortic aneurysm[16]. In that study, aortic aneurysm was defined as discharge from hospital or death due to abdominal aortic aneurysm[16].

As for aortic dissection, few epidemiologic studies were conducted. The aforementioned ecological regression analysis based on international databases suggested no association between a temporal trend in BMI and a temporal trend in age-standardized mortality from aortic dissection in men ($P = 0.05$), but it showed a linear inverse association in women ($P = 0.03$)[12].

**Table 4.** Age- adjusted and area- stratified, and multivariable hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality from aortic aneurysm and aortic dissection, JACC study, 37,286 ever smokers and 66,686 never smokers

| | Body Mass Index (kg/ m$^2$) | | | | | |
|---|---|---|---|---|---|---|
| Ever smokers | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | Trend *P* |
| **Men** | 7,133 | 7,348 | 6,834 | 6,673 | 5,554 | |
| Person-years | 101,724 | 114,610 | 108,706 | 107,931 | 90,186 | |
| Total aortic disease (*n*) | 17 | 35 | 32 | 31 | 30 | |
| Multivariable* HR (95%CI) | 1.0 | 2.14 (1.20-3.84) | 2.09 (1.16-3.79) | 2.20 (1.21-3.99) | 2.83 (1.54-5.17) | 0.002 |
| **Women** | 883 | 665 | 635 | 661 | 900 | |
| Person-years | 12,898 | 10,506 | 10,176 | 10,231 | 14,121 | |
| Total aortic disease (*n*) | 3 | 3 | 2 | 2 | 5 | |
| Multivariable* HR (95%CI) | 1.0 | 1.69 (0.25-11.56) | 0.53 (0.06-5.12) | 1.64 (0.21-12.78) | 1.93 (0.31-12.07) | 0.53 |
| Never smokers | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | Trend *P* |
| **Men** | 1,775 | 2,042 | 2,164 | 2,286 | 2,128 | |
| Person-years | 26,674 | 33,026 | 35,860 | 37,855 | 35,254 | |
| Total aortic disease (*n*) | 6 | 2 | 5 | 2 | 6 | |
| Multivariable* HR (95%CI) | 1.0 | 0.39 (0.07-2.04) | 1.08 (0.31-3.78) | 0.46 (0.09-2.43) | 1.87 (0.54-6.56) | 0.39 |
| **Women** | 10,878 | 10,742 | 11,306 | 11,193 | 12,172 | |
| Person-years | 172,336 | 179,590 | 189,670 | 187,209 | 203,445 | |
| Total aortic disease (*n*) | 20 | 17 | 17 | 15 | 23 | |
| Multivariable* HR (95%CI) | 1.0 | 0.94 (0.49-1.80) | 0.91 (0.47-1.74) | 0.80 (0.41-1.57) | 1.12 (0.61-2.05) | 0.93 |

*Adjustment for age, alcohol intake, perceived mental stress, walking, sports, educational level, fresh fish intake, and employment status.

We consider that aortic wall degeneration caused by high BMI-related inflammation could partly explain the BMI–aortic disease association pathologically. Aortic disease—dilation, dissection, and rupture of the aorta—is caused by the structural and functional consequences of weakening of the aortic wall8). The aortic wall is composed of vascular smooth muscle cells and an extracellular matrix, which are responsible for its resistance to rapid arterial flow and high pressure8). The histologic features of aortic disease are death of the vascular smooth muscle cells and destruction of the extracellular matrix, i.e., elastin fragmentation or collagen degradation in the aortic media and adventitia4, 8). These degenerations of the aortic wall may be dependent on proteases, inflammatory cells, and inflammatory cytokines8). The possible source of these inflammatory molecules is the peripheral vascular adipose tissue (PVAT) surrounding the aortic wall9), which secretes various inflammatory molecules such as proteases (matrix metalloproteinase 9, cathepsin K and S), inflammatory cells (neutrophils, mast cells, and T cells) and cytokines (IL-6), and then induces aneurysmal development. In addition, the Framingham Offspring Cohort Study suggested that the volume of PVAT in both the thorax and the abdomen was correlated with the aortic dimensions17), an important predictor of future abdominal aortic aneurysm18), and that BMI was correlated with the volume of PVAT in the aorta (correlation coefficient $=0.53$, $P < 0.001$)10). However, limited evidence exists regarding the involvement of PVAT associated with high BMI in the development of aneurysm and dissection. Another possibility is that increased mortality after aneurysm repair surgery may be due in part to the complications along with severe obesity. A retrospective study using a US database with 2,097 open and 3,358 endovascular repair surgeries for abdominal aortic aneurysm showed that patients with severe obesity (BMI ≥ 40 kg/m$^2$) demonstrated an excess risk of mortality after open surgery7). Because the number of patients with such severe obesity was only 34 (0.03%) in our cohort, such a possibility is unlikely. These lines of evidence support our results and could explain the mechanisms of the observed association between BMI and aortic aneurysm.

As for aortic dissection, not only aortic wall degeneration but also intimal tear, the entry of blood into the aortic wall separating the intima from the media or adventitia19), is responsible for the early phase of dissection20). Aortic intimal tear is induced by hemodynamic shear stress19), the frictional force acting on the inner vessel wall as a result of the rapid flow of blood21). Shear stress according to the Poiseuille law is proportional to blood flow viscosity and inversely proportional to the third power of the internal radius[21]. A previous cohort study of 1,583 men and women aged 18 to 90 years suggested that BMI was associated with a larger brachial artery diameter[22], probably because an increased lumen diameter with higher BMI may reduce the shear stress on the aortic wall. These findings may partly explain why we did not observe an association between BMI and mortality from aortic dissection.

Also, we found a positive association between BMI and mortality from aortic aneurysm among ever-smokers but not among never-smokers. As described above, high BMI-related inflammation could partly explain the BMI–aortic disease association. Cigarette smoking increases the expression of inflammatory systems such as matrix metalloproteinases as a potential mechanism promoting aortic disease[23], and cigarette smoking may intensify the BMI–aortic disease relationship.

In the present study, a positive association between BMI and aortic disease was observed among men, whilst no association was observed among women. As stated above, the BMI–aortic disease association was observed only among ever-smokers. This could also explain the reasons for the sex difference in risk of mortality from aortic disease according to BMI. When we further conducted a sex-specific smoking-stratified analysis, BMI was or tended to be positively associated with mortality from aortic disease among smokers for both sexes, and no associations were found among never-smokers, regardless of sex.

As for screening for aortic diseases, the United States Preventive Services Task Force recommends screening for abdominal aortic aneurysm based on age, sex, and smoking status[24], and the Japanese Circulation Society recommends screening based on age, sex, smoking status, hypertension, history of cardiovascular disease, and family history[25]. However, this recommendation did not rely on epidemiologic evidence from Japanese populations, which was unavailable. Our study is the first to provide evidence regarding the association of BMI with aortic aneurysm among Japanese men.

Several strengths of the present study should be mentioned. First, this study exhibited a prospective design and a long duration of follow-up. Second, the JACC study is a large, nationwide, community-based Japanese cohort, which allowed us to examine the associations of BMI with aortic diseases for the first time in an Asian population. Third, the lower distribution of BMI in the present study than in previous Western studies enabled us to examine the potential impact of low BMI, which can be difficult to examine in Western populations. Our results may extend the evidence of a BMI–aortic disease association for populations with lower BMI distribution, although the generalizability should be taken into account cautiously.

Several limitations should be addressed. First, our data were based on self-reported height and weight, which was likely to cause measurement errors such as overestimation of height, underestimation of weight, and underestimation of BMI[26]. However, according to the previous studies comparing self-reported and measured height, weight, and BMI among British participants aged 35 to 76 years[26] and Japanese participants aged 40 to 59 years[27], normal BMI category participants were the least likely to be incorrectly allocated to another BMI category, and underweight participants were also less likely to be misclassified into the normal range than overweight/obese participants. Second, the number of aortic disease cases among our participants was modest, although it yielded sufficient numbers to detect significant associations. The JACC Study involved the largest number of deceased cases of aortic disease to date in Japan[28]. Third, we ascertained aortic disease on the basis of death certificates, but data related to imaging studies or autopsy were unavailable. However, according to a hospital-based autopsy study, little misclassification exists between the diagnoses of aortic aneurysm and dissection based on the death certificate and those based on clinical and autopsy-derived information[29]. Fourth, an aortic aneurysm whose site was not described on the death certificate was classified into aortic aneurysm of unspecified site, which comprised 5% in the present study. The results did not change after the exclusion of aortic aneurysm of unspecified site: the multivariable HRs (95% CI) for each quintile compared with the lowest quintiles of BMI for aortic aneurysm were 2.66 (1.21–5.85) in the second quintile; 3.01 (1.37–6.61) in the third; 3.94 (1.81–8.56) in the fourth; and 4.73 (2.14–10.46) in the highest quintile; $P$ for trend $<$ 0.01 among men and 0.55 (0.19–1.60) in the second quintile; 0.56 (0.19–1.63) in the third; 0.33 (0.09–1.20) in the fourth; and 1.05 (0.45–2.47) in the highest quintile; $P$ for trend$=$0.72 among women. Lastly, the exposure examination was limited to that at baseline. Changes in the exposures of interest over time would have led our estimates towards the null value.

## Conclusion

We found a positive association between BMI and mortality from aortic disease, especially for thoracic and abdominal aortic aneurysms among men and smokers in a large, nationwide, community-based Japanese cohort. This observation expands the evidence on a BMI–aortic disease association with leaner populations, such as Asian populations.

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## COI Disclosure

The authors declared no conflict of interest.

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**Supplemental Table 1.** Age- adjusted and area- stratified, and multivariable hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality from aortic aneurysm and aortic dissection, JACC study, 43,937 men and 60,035 women, adjusting further for hypertension, hyperlipidemia, and diabetes mellitus

| | Body Mass Index (kg/m$^2$) | | | | | |
|---|---|---|---|---|---|---|
| Men | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | Trend *P* |
| Person-years | 128,397 | 147,636 | 144,567 | 145,786 | 125,440 | |
| Total aortic disease (*n*) | 23 | 37 | 37 | 33 | 36 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 1.61 (0.95-2.71) | 1.74 (1.03-2.94) | 1.67 (0.97-2.85) | 2.30 (1.36-3.92) | 0.004 |
| Multivariable* HR (95%CI) | 1.0 | 1.64 (0.97-2.78) | 1.76 (1.04-2.98) | 1.70 (0.99-2.92) | 2.26 (1.32-3.87) | 0.006 |
| Total aortic aneurysm (*n*) | 10 | 22 | 21 | 25 | 22 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 2.34 (1.10-4.95) | 2.47 (1.16-5.28) | 3.22 (1.54-6.74) | 3.70 (1.74-7.87) | <.0001 |
| Multivariable* HR (95%CI) | 1.0 | 2.41 (1.13-5.12) | 2.56 (1.20-5.49) | 3.44 (1.63-7.25) | 3.96 (1.84-8.52) | <.0001 |
| Thoracic aortic aneurysm (*n*) | 2 | 5 | 8 | 10 | 7 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 2.75 (0.53-14.21) | 4.87 (1.03-23.13) | 6.42 (1.39-29.54) | 6.01 (1.23-29.35) | 0.01 |
| Multivariable* HR (95%CI) | 1.0 | 2.57 (0.49-13.50) | 4.89 (1.02-23.56) | 6.61 (1.40-31.10) | 5.19 (1.04-25.90) | 0.02 |
| Abdominal aortic aneurysm (*n*) | 6 | 15 | 12 | 13 | 11 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 2.61 (1.01-6.77) | 2.28 (0.85-6.10) | 2.77 (1.04-7.35) | 3.05 (1.12-8.34) | 0.04 |
| Multivariable* HR (95%CI) | 1.0 | 2.80 (1.08-7.30) | 2.40 (0.89-6.48) | 3.17 (1.18-8.46) | 3.67 (1.33-10.17) | 0.01 |
| Aortic dissection (*n*) | 13 | 15 | 16 | 8 | 14 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 1.06 (0.51-2.24) | 1.18 (0.57-2.47) | 0.61 (0.25-1.49) | 1.30 (0.60-2.81) | 0.98 |
| Multivariable* HR (95%CI) | 1.0 | 1.05 (0.49-2.22) | 1.12 (0.53-2.36) | 0.55 (0.22-1.36) | 1.15 (0.52-2.52) | 0.70 |

| Women | < 20.3 | 20.3-21.9 | 21.9-23.3 | 23.3-25.1 | ≥ 25.1 | Trend *P* |
|---|---|---|---|---|---|---|
| Person-years | 185,234 | 190,096 | 199,846 | 197,440 | 217,566 | |
| Total aortic disease (*n*) | 23 | 20 | 19 | 17 | 28 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 0.98 (0.54-1.78) | 0.89 (0.49-1.65) | 0.81 (0.43-1.52) | 1.20 (0.68-2.10) | 0.80 |
| Multivariable* HR (95%CI) | 1.0 | 0.91 (0.50-1.66) | 0.82 (0.45-1.52) | 0.73 (0.39-1.39) | 0.97 (0.55-1.72) | 0.68 |
| Total aortic aneurysm (*n*) | 12 | 6 | 6 | 3 | 12 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 0.59 (0.22-1.57) | 0.58 (0.22-1.56) | 0.29 (0.08-1.05) | 1.05 (0.46-2.40) | 0.59 |
| Multivariable* HR (95%CI) | 1.0 | 0.55 (0.20-1.49) | 0.55 (0.20-1.49) | 0.26 (0.07-0.93) | 0.81 (0.35-1.88) | 0.29 |
| Thoracic aortic aneurysm (*n*) | 5 | 3 | 2 | 1 | 8 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 0.68 (0.16-2.87) | 0.44 (0.09-2.30) | 0.22 (0.03-1.91) | 1.61 (0.51-5.07) | 0.91 |
| Multivariable* HR (95%CI) | 1.0 | 0.56 (0.13-2.44) | 0.38 (0.07-2.01) | 0.19 (0.02-1.72) | 1.28 (0.39-4.20) | 0.74 |
| Abdominal aortic aneurysm (*n*) | 6 | 2 | 3 | 2 | 4 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 0.41 (0.08-2.02) | 0.63 (0.16-2.53) | 0.42 (0.08-2.11) | 0.75 (0.20-2.75) | 0.74 |
| Multivariable* HR (95%CI) | 1.0 | 0.39 (0.07-2.11) | 0.75 (0.18-3.24) | 0.36 (0.07-1.93) | 0.51 (0.13-2.06) | 0.41 |
| Aortic dissection (*n*) | 11 | 14 | 13 | 14 | 16 | |
| Age-adjusted, area- stratified HR (95%CI) | 1.0 | 1.40 (0.63-3.09) | 1.24 (0.55-2.77) | 1.34 (0.61-2.98) | 1.39 (0.64-3.03) | 0.48 |
| Multivariable* HR (95%CI) | 1.0 | 1.33 (0.60-2.95) | 1.15 (0.51-2.58) | 1.25 (0.56-2.77) | 1.15 (0.52-2.54) | 0.81 |

*Adjustment for age, alcohol intake, cigarette smoking status, perceived mental stress, walking, sports, educational level, fresh fish intake, employment status, hypertension, hyperlipidemia, and diabetes mellitus..