

# Height and Mortality from Aortic Aneurysm and Dissection

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**Aims:** Reports on the association between height and aortic disease have been modest, and there are only a few studies investigating the association between height and mortality from specific aortic disease types or by sex.

**Methods:** We conducted the Japan Collaborative Cohort Study, a prospective study of 99,067 Japanese (41,730 men and 57,337 women) aged 40–79 years old. Height was self-reported, and the participants were followed up from 1988–1989 to the end of 2009. Sex-specific hazard ratios (95% confidence intervals) of mortality from aortic disease type according to sex-specific quartiles of height were analyzed using the Cox proportional hazards model.

**Results:** During the median follow-up period of 19.1 years, the numbers of deaths due to aortic aneurysm, thoracic aortic aneurysm, abdominal aortic aneurysm, and aortic dissection were 87, 29, 48, and 56 among men and 35, 17, 15, and 65 among women, respectively. The sex-specific multivariate hazard ratios (95% confidence intervals) and *p* for trend for the highest versus lowest quartiles of height were 1.10 (0.66–1.83), *p*=0.58 among men and 1.54 (0.85–2.79), *p*=0.06 among women for total aortic disease; 1.85 (0.80–4.28), *p*=0.16 among men and 5.67 (0.90–35.77), *p*=0.08 among women for abdominal aortic aneurysm; and 1.13 (0.48–2.64), *p*=0.65 among men and 1.70 (0.82–3.50), *p*=0.04 among women for aortic dissection. The positive association was observed for both sexes, albeit more prominent among women. No association was found between height and mortality from thoracic aortic aneurysms.

**Conclusions:** As per our findings, we were able to determine that height was positively associated with mortality from abdominal aortic aneurysm in the Japanese population.

**Key words:** Epidemiology, Aortic disease, Aneurysm, Dissection, Height

## Introduction

Aortic disease, including aortic aneurysm and dissection, is a life-threatening disease with high fatality once rupture or complications occur<sup>1, 2</sup>. The precise mechanisms leading to aortic disease remain unclear; however, biomechanical wall stress that exceeds the mechanical strength of the arterial wall has been determined as the final common pathway<sup>3-5</sup>. Taller height is one of the factors that could elevate peak wall stress in the aorta<sup>6</sup>.

The results of epidemiologic prospective studies regarding the association between height and aortic disease have been modest. One meta-analysis comprising 121 prospective studies of 1,085,949 participants (60% in Europe or 33% in North America) and one prospective study of 18,403 British men aged 40–64 years old reported that height was positively associated with mortality from aortic aneurysm<sup>7, 8</sup>, while another prospective study of 8,361 British men aged 16–30 years old reported a positive but non-significant association between height and

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mortality from aortic aneurysm<sup>9</sup>). As regards incident aortic disease, 3 prospective studies of 161,808 American women aged 50–79 years old, 104,813 American men and women aged over 18 years old, and 15,792 American men and women aged 45–64 years old reported a positive association between height and risk of abdominal aortic aneurysm (AAA)<sup>10–12</sup>. Another prospective study of 7,682 men of Japanese ancestry in Hawaii aged 46–65 years old reported a positive association between height and risk of incident aortic aneurysm, but not of incident aortic dissection (AD)<sup>13</sup>.

Aortic diseases [thoracic aortic aneurysm (TAA), AAA, and AD] share common risk factors such as hypertension<sup>14–16</sup>, smoking<sup>17</sup>, obesity<sup>15, 16</sup>, and inflammation<sup>18, 19</sup>, but the magnitude of the association between risk factors and aortic diseases may not be uniform across disease types due to some etiological differences. For example, high body mass index (BMI) was associated with mortality from aortic aneurysms, but not AD<sup>20</sup>. As for height, it has been suggested that taller height may increase the risk of aortic disease by augmenting biomechanical wall stress<sup>6</sup>. However, since the magnitude of biomechanical wall stress<sup>21, 22</sup> and the mechanical strength of aortic wall<sup>23, 24</sup> differ according to aortic regions, the association between height and risk of aortic diseases would vary by the disease types. To date, only one study was able to examine height and aortic disease types (aortic aneurysm and AD)<sup>13</sup>, and no study has examined all three types of aortic disease (TAA, AAA, and AD) in the same population. In addition, previous studies have shown only male or sex-combined results, although mechanical wall stress could be greater in women than in men<sup>6</sup>. Therefore, the strength of the association between height and risk of aortic disease may differ between men and women.

## Aim

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 numbers of participants in Asia. In this study, we aimed to examine the sex-specific associations between height and mortality from aortic disease by type (total aortic disease, total aortic aneurysm, TAA, AAA, and AD) in this Japanese community-based 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 in Japan. The prospective study participants were aged 40–79 years old during the baseline period (1988–1990), and they completed self-administered questionnaires concerning their lifestyles and medical histories regarding previous cardiovascular disease or cancer<sup>25</sup>. However, the following participants were excluded from the study: 6,057 participants for whom the self-reported height was missing or inappropriate and 5,461 with a history of cardiovascular disease or cancer. As a result, 99,067 persons (41,730 men and 57,337 women) were included in the analysis. Written or explicit verbal informed consent was obtained before the participants completed the questionnaire. In several communities, informed consent was obtained from community leaders rather than from individual participants, which was a common practice regarding informed consent in Japan before the Ethical Guidelines for Epidemiological Studies came into effect in 2002. Individual informed consent was obtained from 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 Ethical Committees of Hokkaido University, Osaka University, and the University of Tsukuba.

### Mortality Surveillance

In each community, the investigators conducted a systematic review of death certificates. In Japan, registration of death is legally required and is reportedly adhered to countrywide. Thus, all deaths that occurred in the cohort were ascertained by death certificates obtained from public health centers, except for those of participants who moved out from their original community during follow-up (5.7%), in which case the participant was censored. Data on community-to-community movement were verified using population-register sheets. For each participant, the person-years of follow-up were tallied from the date the baseline questionnaire was completed to the date of mortality from aortic disease, death from another cause, or moving out of the community to the end of 2009, whichever preceded, except for areas in which the follow-up ended earlier, that is, four areas in 1999, four in 2003, and two in 2008. The median follow-up period was 19.1 years. We used the underlying cause of death coded by the International Statistical Classification of Diseases and Related Health Problems (10th Revision) to identify mortality endpoints as follows: I711 to I712 for TAA, I713 to I714 for AAA, I715 to I716 for thoracoabdominal aortic aneurysm, I718 to I719 for aortic aneurysm of

unspecified site, I711 to I719 for total aortic aneurysm, I710 for AD, and I710 to I719 for total aortic disease.

### Measurements

The participants were requested to enter their height (cm) during the previous year in the baseline questionnaire. Various questions regarding life-style were also posed in the baseline questionnaire, including questions on age, sex, weight, smoking status, alcohol intake, perceived mental stress, walking, sports, fresh fish intake, employment status, and education level (the age of the highest level of school attained).

### Statistical Analysis

The analysis of covariance was used to test for differences in age-adjusted means and prevalence of baseline characteristics according to sex-specific quartiles of height. Hazard ratios (HRs) with 95% confidence intervals (CIs) for each quartile compared with the lowest quartile were calculated after stratification by area and adjustments for sex, age, and other potential confounding factors using Cox proportional hazards survival models. Potential confounding factors included the following: quartile of BMI which was calculated as body weight (kg) divided by the square of the height (m<sup>2</sup>); smoking status (never, former smoker, and current smoker of 1–19 or ≥ 20 cigarettes/day); alcohol intake (never, former drinker, and 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); and employment status (full-time worker, part-time worker, independent business, full-time homemaker, unemployed, or others). Indicator variables were used for missing variables. The linear trend of the HRs across the quartiles was tested using variables with -3, -1, 1, and 3 assigned to successive quartiles. Multiplicative interactions with sex and dummy variables of height in relation to mortality from aortic diseases were tested using a cross-product term. We then further examined the association between height and mortality from aortic disease using Fine and Gray models to account for the competing risk of pre-aortic disease mortality from stroke, coronary heart disease, or cancer by considering the subdistribution HR (sHR)<sup>26</sup>. As the

causal pathway, we added adjustment variables (quartiles of systolic blood pressure, diastolic blood pressure, total cholesterol, and triglyceride, available in 28,110 subsamples) in the multivariable model.

We then used SAS version 9.4 (SAS Institute, Cary, NC, USA) for the analyses. All probability values for the statistical tests were two-tailed, and values below 0.05 were regarded as significant.

## Results

During a median follow-up period of 19.1 years of 99,067 participants, we documented 122 deaths due to aortic aneurysm (46 TAAs, 63 AAAs, 6 thoracoabdominal aortic aneurysms, and 7 aortic aneurysms of unspecified sites) and 121 deaths due to AD.

The baseline characteristics of this study cohort according to height quartiles are shown in **Table 1**. Age and BMI were found to be inversely correlated with height in both men and women. Current drinking, current smoking, high perceived mental stress, and college or higher education was positively correlated with height in both men and women. Walking, exercise, and fresh fish intake were positively correlated with height in men, but those except for exercise were inversely correlated in women.

As shown in **Table 2**, height was positively associated with mortality from aortic disease, especially for AAA. A non-significant and non-linear positive trend was observed between height and mortality from total aortic disease and AD. Further, no association was noted between height and mortality due to TAA. The multivariate HRs (95% CI) for the 2nd, 3rd, and the highest quartiles compared with the lowest quartiles of height and 10 cm increment of height were 1.05 (0.75–1.49), 1.44 (1.01–2.05), and 1.29 (0.88–1.89) (*p* for trend=0.08) and 1.22 (0.98–1.51) for total aortic disease; 1.55 (0.79–3.04), 1.60 (0.76–3.38), and 2.21 (1.05–4.62) (*p* for trend=0.04) and 1.76 (1.17–2.66) for AAA; and 1.05 (0.62–1.77), 1.81 (1.09–3.00), and 1.45 (0.83–2.51) (*p* for trend=0.06) and 1.34 (0.99–1.82) for AD, respectively.

Similar results were observed when systolic blood pressure, diastolic blood pressure, total cholesterol, and triglyceride, as potential mediating factors between height and aortic disease, were adjusted for; the multivariable HRs (95% CI) in the 2nd, 3rd, and the highest versus the lowest quartile of height were 1.05 (0.74–1.49), 1.44 (1.01–2.04), and 1.29 (0.88–1.90), *p* for trend=0.08 for total aortic disease and 1.55 (0.79–3.05), 1.57 (0.74–3.33), and 2.25 (1.07–4.73), *p* for trend=0.04 for AAA (data not shown).

After the competing risk of pre-aortic disease

**Table 1.** Age-adjusted baseline characteristics and 95% confidence intervals according to quartiles of height, 41,730 men and 57,337 women, JACC Study

| Men                                | Height (cm)         |                     |                     |                     |
|------------------------------------|---------------------|---------------------|---------------------|---------------------|
|                                    | < 159.0             | 159.1-163.0         | 163.1-167.0         | ≥ 167.1             |
| <b>No. at risk</b>                 | 10,651              | 11,419              | 9,415               | 10,245              |
| Age at baseline, years             | 61.7 (61.5-61.9)    | 57.7 (57.6-57.9)    | 55.8 (55.6-56.0)    | 52.3 (52.1-52.5)    |
| Height, cm                         | 154.8 (154.8-154.9) | 161.3 (161.3-161.4) | 165.3 (165.2-165.3) | 171.0 (170.9-171.1) |
| Body mass index, kg/m <sup>2</sup> | 22.9 (22.9-23.0)    | 22.6 (22.6-22.7)    | 22.6 (22.5-22.6)    | 22.4 (22.4-22.5)    |
| Current drinkers, %                | 68.8 (67.8-69.7)    | 70.7 (69.8-71.6)    | 72.2 (71.2-73.3)    | 73.2 (72.2-74.2)    |
| Current smokers, %                 | 53.5 (52.5-54.4)    | 53.6 (52.6-54.5)    | 54.4 (53.4-55.4)    | 55.0 (54.0-56.0)    |
| High perceived mental stress, %    | 20.3 (19.3-21.3)    | 22.0 (21.1-22.9)    | 23.0 (22.1-24.0)    | 26.6 (25.6-27.5)    |
| Walking ≥ 30min/day, %             | 87.0 (86.3-87.8)    | 87.6 (86.9-88.3)    | 87.9 (87.2-88.7)    | 87.8 (87.1-88.5)    |
| Exercise ≥ 5h/week, %              | 7.0 (6.4-7.6)       | 6.9 (6.3-7.4)       | 6.9 (6.4-7.5)       | 7.8 (7.3-8.4)       |
| College or higher education, %     | 10.7 (9.8-11.5)     | 16.7 (15.9-17.6)    | 19.1 (18.2-20.0)    | 24.5 (23.6-25.3)    |
| Fresh fish intake, times/week      | 3.4 (3.4-3.5)       | 3.5 (3.4-3.5)       | 3.6 (3.5-3.6)       | 3.5 (3.5-3.6)       |
| Unemployed, %                      | 16.6 (15.8-17.3)    | 15.2 (14.5-15.8)    | 16.0 (15.2-16.7)    | 17.4 (16.7-18.1)    |
| Systolic blood pressure, mmHg      | 135.4 (134.7-136.0) | 134.9 (134.2-135.6) | 134.9 (134.1-135.7) | 134.8 (133.9-135.7) |
| Diastolic blood pressure, mmHg     | 80.3 (79.9-80.7)    | 81.0 (80.6-81.4)    | 81.4 (81.0-81.9)    | 81.6 (81.1-82.1)    |
| Total cholesterol, mg/dL           | 188.1 (186.9-189.3) | 188.0 (186.7-189.3) | 188.0 (186.5-189.5) | 187.6 (185.9-189.3) |
| Triglyceride, mg/dl                | 129.2 (124.3-134.1) | 133.5 (128.6-138.3) | 127.6 (122.2-133.0) | 135.5 (129.9-141.2) |

  

| Women                              | < 147.9             | 148.0-150.9         | 151.0-154.9         | ≥ 155.0             |
|------------------------------------|---------------------|---------------------|---------------------|---------------------|
| <b>No. at risk</b>                 | 13,934              | 14,211              | 13,391              | 15,801              |
| Age at baseline, years             | 62.2 (62.0-62.3)    | 58.5 (58.3-58.6)    | 55.2 (55.1-55.4)    | 53.0 (52.9-53.1)    |
| Height, cm                         | 143.8 (143.7-143.8) | 149.3 (149.3-149.4) | 152.5 (152.5-152.6) | 157.9 (157.8-157.9) |
| Body mass index, kg/m <sup>2</sup> | 23.3 (23.3-23.4)    | 23.0 (23.0-23.1)    | 22.9 (22.8-22.9)    | 22.5 (22.5-22.6)    |
| Current drinkers, %                | 12.3 (11.6-12.9)    | 14.2 (13.6-14.9)    | 16.1 (15.4-16.7)    | 17.2 (16.6-17.8)    |
| Current smokers, %                 | 4.4 (4.0-4.8)       | 5.4 (5.0-5.8)       | 5.1 (4.7-5.5)       | 6.5 (6.1-6.8)       |
| High perceived mental stress, %    | 18.6 (17.8-19.4)    | 19.4 (18.6-20.2)    | 21.0 (20.2-21.8)    | 21.7 (20.9-22.4)    |
| Walking ≥ 30min/day, %             | 89.0 (88.4-89.7)    | 89.5 (88.9-90.1)    | 89.4 (88.8-90.0)    | 89.4 (88.8-90.0)    |
| Exercise ≥ 5h/week, %              | 4.6 (4.2-5.0)       | 4.3 (3.9-4.7)       | 4.5 (4.2-4.9)       | 4.6 (4.3-5.0)       |
| College or higher education, %     | 6.5 (5.9-7.1)       | 9.1 (8.6-9.7)       | 11.2 (10.7-11.8)    | 13.1 (12.6-13.7)    |
| Fresh fish intake, times/week      | 3.5 (3.4-3.5)       | 3.5 (3.5-3.6)       | 3.6 (3.6-3.6)       | 3.6 (3.5-3.6)       |
| Unemployed, %                      | 21.6 (20.9-22.3)    | 19.4 (18.8-20.0)    | 18.2 (17.6-18.9)    | 20.0 (19.5-20.6)    |
| Systolic blood pressure, mmHg      | 132.5 (132.0-133.0) | 131.1 (130.6-131.7) | 131.0 (130.5-131.6) | 130.6 (130.0-131.2) |
| Diastolic blood pressure, mmHg     | 77.7 (77.4-78.0)    | 78.0 (77.6-78.3)    | 78.2 (77.9-78.6)    | 78.3 (78.0-78.7)    |
| Total cholesterol, mg/dL           | 202.8 (201.8-203.9) | 205.4 (204.3-206.5) | 204.6 (203.6-205.7) | 203.0 (201.9-204.2) |
| Triglyceride, mg/dl                | 113.8 (111.0-116.7) | 115.1 (112.2-117.9) | 111.8 (109.0-114.5) | 110.6 (107.9-113.3) |

\*The analysis of covariance was used for the statistical test. All *p* values for difference were < 0.001.

mortality from stroke, coronary heart disease, or cancer was considered, height has remained to be positively associated with mortality from AAA; sHRs (95% CI) in the 2nd, 3rd, and the highest versus lowest quartiles of height and 10 cm increment of height were 1.55 (0.79–3.07), 1.62 (0.76–3.45), and 2.18 (1.04–4.57) (*p* for trend=0.05) and 1.76 (1.20–2.58) for AAA. A non-significant and non-linear positive trend between height and mortality from total aortic disease and AD was also remained; sHRs (95% CI) in the 2nd, 3rd, and the highest versus lowest quartiles of height and 10cm increment of height were

1.05 (0.74–1.49), 1.44 (1.00–2.07), and 1.26 (0.85–1.86) (*p* for trend=0.12) and 1.21 (0.98–1.50) for total aortic disease and 1.04 (0.62–1.75), 1.81 (1.08–3.03), and 1.41 (0.81–2.46) (*p* for trend=0.08) and 1.33 (1.01–1.76) for AD. The results remained unchanged when we considered the competing risk of total mortality from diseases other than aortic disease.

The association was approximately the same for both men and women, although it was more prominent among women; the multivariate HRs (95% CI) in the 2nd, 3rd, and the highest versus the lowest quartile of height and 10 cm increment of height were



**Table 2.** 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

|   | Men and Women                    |                  |                  |                  | <i>P</i> for trend | per 10cm         |
|---|----------------------------------|------------------|------------------|------------------|--------------------|------------------|
|   | Sex-specific quartiles of height |                  |                  |                  |                    |                  |
|   | 1st quartile                     | 2nd quartile     | 3rd quartile     | 4th quartile     |                    |                  |
| <b>No. at risk</b>                                  | 24,585                           | 25,630           | 22,806           | 26,046           |                    |                  |
| <b>Person-years</b>                                 | 378,362                          | 417,125          | 382,217          | 443,796          |                    |                  |
| <b>Total aortic disease (n)</b>                     | 70                               | 63               | 61               | 49               |                    |                  |
| Crude mortality rate per 1000 person-years          | 0.19                             | 0.15             | 0.16             | 0.11             |                    |                  |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0                              | 1.04 (0.74-1.47) | 1.41 (0.99-2.00) | 1.26 (0.86-1.85) | 0.11               | 1.19 (0.96-1.47) |
| Multivariable* HR (95%CI)                           | 1.0                              | 1.05 (0.75-1.49) | 1.44 (1.01-2.05) | 1.29 (0.88-1.89) | 0.08               | 1.22 (0.98-1.51) |
| Multivariable* sHR (95% CI)                         | 1.0                              | 1.05 (0.74-1.49) | 1.44 (1.00-2.07) | 1.26 (0.85-1.86) | 0.12               | 1.21 (0.98-1.50) |
| <b>Total aortic aneurysm (n)</b>                    | 41                               | 35               | 25               | 21               |                    |                  |
| Crude mortality rate per 1000 person-years          | 0.11                             | 0.08             | 0.07             | 0.05             |                    |                  |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0                              | 1.04 (0.66-1.64) | 1.09 (0.66-1.81) | 1.11 (0.64-1.91) | 0.69               | 1.07 (0.80-1.43) |
| Multivariable* HR (95%CI)                           | 1.0                              | 1.07 (0.68-1.70) | 1.12 (0.67-1.87) | 1.13 (0.65-1.95) | 0.65               | 1.10 (0.82-1.47) |
| Multivariable* sHR (95% CI)                         | 1.0                              | 1.07 (0.67-1.70) | 1.12 (0.66-1.90) | 1.11 (0.63-1.95) | 0.71               | 1.10 (0.81-1.50) |
| <b>Thoracic aortic aneurysm (n)</b>                 | 20                               | 11               | 9                | 6                |                    |                  |
| Crude mortality rate per 1000 person-years          | 0.05                             | 0.03             | 0.02             | 0.01             |                    |                  |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0                              | 0.65 (0.31-1.36) | 0.76 (0.34-1.70) | 0.59 (0.23-1.53) | 0.36               | 0.72 (0.45-1.13) |
| Multivariable* HR (95%CI)                           | 1.0                              | 0.66 (0.31-1.40) | 0.75 (0.33-1.69) | 0.60 (0.23-1.56) | 0.36               | 0.75 (0.48-1.16) |
| Multivariable* sHR (95% CI)                         | 1.0                              | 0.66 (0.31-1.41) | 0.74 (0.31-1.74) | 0.58 (0.22-1.58) | 0.35               | 0.75 (0.49-1.14) |
| <b>Abdominal aortic aneurysm (n)</b>                | 16                               | 19               | 13               | 15               |                    |                  |
| Crude mortality rate per 1000 person-years          | 0.04                             | 0.05             | 0.03             | 0.03             |                    |                  |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0                              | 1.48 (0.76-2.90) | 1.52 (0.72-3.21) | 2.14 (1.04-4.44) | 0.05               | 1.67 (1.13-2.48) |
| Multivariable* HR (95%CI)                           | 1.0                              | 1.55 (0.79-3.04) | 1.60 (0.76-3.38) | 2.21 (1.05-4.62) | 0.04               | 1.76 (1.17-2.66) |
| Multivariable* sHR (95% CI)                         | 1.0                              | 1.55 (0.79-3.07) | 1.62 (0.76-3.45) | 2.18 (1.04-4.57) | 0.05               | 1.76 (1.20-2.58) |
| <b>Aortic dissection (n)</b>                        | 29                               | 28               | 36               | 28               |                    |                  |
| Crude mortality rate per 1000 person-years          | 0.08                             | 0.07             | 0.09             | 0.06             |                    |                  |
| Age- and sex- adjusted, area- stratified HR (95%CI) | 1.0                              | 1.04 (0.62-1.76) | 1.78 (1.08-2.94) | 1.43 (0.83-2.47) | 0.07               | 1.33 (0.98-1.81) |
| Multivariable* HR (95%CI)                           | 1.0                              | 1.05 (0.62-1.77) | 1.81 (1.09-3.00) | 1.45 (0.83-2.51) | 0.06               | 1.34 (0.99-1.82) |
| Multivariable* sHR (95% CI)                         | 1.0                              | 1.04 (0.62-1.75) | 1.81 (1.08-3.03) | 1.41 (0.81-2.46) | 0.08               | 1.33 (1.01-1.76) |

CI, confidence interval; HR indicates hazard ratio; and sHR, subdistribution hazard ratio.

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

1.10 (0.63–1.94), 1.85 (1.06–3.24), and 1.54 (0.85–2.79) (*p* for trend=0.06) and 1.33 (0.94–1.88) for total aortic disease; 4.54 (0.84–24.58), 4.19 (0.63–27.97), and 5.67 (0.90–35.77) (*p* for trend=0.08) and 2.64 (1.15–6.06) for AAA; and 0.85 (0.40–1.81), 2.05 (1.03–4.05), and 1.70 (0.82–3.50) (*p* for trend=0.04) and 1.44 (0.93–2.23) for AD (shown in [Table 3](#)). The associations were found to be less prominent among men; the respective HRs (95% CI) were 1.00 (0.65–1.56), 1.19 (0.75–1.89), and 1.10 (0.66–1.83) (*p* for trend=0.58) and 1.13 (0.86–1.49) for total aortic disease; 1.21 (0.56–2.60), 1.32 (0.57–3.05), and 1.85 (0.80–4.28) (*p* for trend=0.16) and 1.53 (0.96–2.45) for AAA; and 1.19 (0.56–2.50), 1.55 (0.73–3.30), and 1.13 (0.48–2.64) (*p* for trend=0.65) and 1.24 (0.79–1.93) for AD. No interaction between

height and sex was observed in relation to total aortic aneurysm (*p* for interaction=0.68), AAA (*p* for interaction=0.60), and AD (*p* for interaction=0.72).

## Discussion

In this large, community-based, prospective cohort study, we observed generally positive associations between height and mortality risk from AAA. There was a non-significant and non-linear positive trend between height and mortality from total aortic disease and AD. The positive association was observed for both men and women, though it was more prominent among women. As regards TAA, height was determined to be not associated with mortality. These associations were not altered when

**Table 3.** 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

|  | Men and Women |                   |                   |                   | P for trend | per 10cm         |
|--|---------------|-------------------|-------------------|-------------------|-------------|------------------|
|  | Height (cm)   |                   |                   |                   |             |                  |
| Men  | < 159.0       | 159.1-163.0       | 163.1-167.0       | ≥ 167.1           |             |                  |
| <b>No. at risk</b>                         | 10,651        | 11,419            | 9,415             | 10,245            |             |                  |
| <b>Person-years</b>                        | 158,108       | 182,023           | 153,398           | 172,286           |             |                  |
| <b>Total aortic disease (n)</b>            | 44            | 39                | 34                | 26                |             |                  |
| Crude mortality rate per 1000 person-years | 0.28          | 0.21              | 0.22              | 0.15              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 0.99 (0.64-1.52)  | 1.18 (0.75-1.86)  | 1.06 (0.64-1.75)  | 0.67        | 1.11 (0.85-1.44) |
| Multivariable* HR (95%CI)                  | 1.0           | 1.00 (0.65-1.56)  | 1.19 (0.75-1.89)  | 1.10 (0.66-1.83)  | 0.58        | 1.13 (0.86-1.49) |
| Multivariable* sHR (95% CI)                | 1.0           | 0.99 (0.64-1.55)  | 1.19 (0.75-1.91)  | 1.06 (0.62-1.80)  | 0.68        | 1.13 (0.85-1.49) |
| <b>Total aortic aneurysm (n)</b>           | 31            | 23                | 18                | 15                |             |                  |
| Crude mortality rate per 1000 person-years | 0.2           | 0.13              | 0.12              | 0.09              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 0.87 (0.51-1.51)  | 0.99 (0.55-1.78)  | 1.03 (0.54-1.94)  | 0.85        | 1.02 (0.73-1.43) |
| Multivariable* HR (95%CI)                  | 1.0           | 0.92 (0.53-1.60)  | 1.02 (0.56-1.86)  | 1.09 (0.57-2.09)  | 0.72        | 1.07 (0.76-1.50) |
| Multivariable* sHR (95% CI)                | 1.0           | 0.91 (0.52-1.60)  | 1.03 (0.56-1.90)  | 1.06 (0.54-2.11)  | 0.78        | 1.07 (0.75-1.53) |
| <b>Thoracic aortic aneurysm (n)</b>        | 13            | 7                 | 5                 | 4                 |             |                  |
| Crude mortality rate per 1000 person-years | 0.08          | 0.04              | 0.03              | 0.02              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 0.59 (0.23-1.50)  | 0.60 (0.21-1.72)  | 0.60 (0.19-1.93)  | 0.43        | 0.80 (0.45-1.40) |
| Multivariable* HR (95%CI)                  | 1.0           | 0.59 (0.23-1.52)  | 0.61 (0.21-1.78)  | 0.61 (0.19-1.99)  | 0.45        | 0.83 (0.47-1.44) |
| Multivariable* sHR (95% CI)                | 1.0           | 0.61 (0.23-1.59)  | 0.63 (0.21-1.86)  | 0.60 (0.17-2.21)  | 0.48        | 0.83 (0.48-1.43) |
| <b>Abdominal aortic aneurysm (n)</b>       | 14            | 13                | 10                | 11                |             |                  |
| Crude mortality rate per 1000 person-years | 0.09          | 0.07              | 0.07              | 0.06              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 1.14 (0.53-2.43)  | 1.27 (0.55-2.89)  | 1.70 (0.75-3.85)  | 0.20        | 1.42 (0.91-2.22) |
| Multivariable* HR (95%CI)                  | 1.0           | 1.21 (0.56-2.60)  | 1.32 (0.57-3.05)  | 1.85 (0.80-4.28)  | 0.16        | 1.53 (0.96-2.45) |
| Multivariable* sHR (95% CI)                | 1.0           | 1.25 (0.57-2.75)  | 1.37 (0.59-3.20)  | 1.84 (0.78-4.36)  | 0.16        | 1.55 (1.01-2.36) |
| <b>Aortic dissection (n)</b>               | 13            | 16                | 16                | 11                |             |                  |
| Crude mortality rate per 1000 person-years | 0.08          | 0.09              | 0.10              | 0.06              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 1.23 (0.59-2.58)  | 1.58 (0.75-3.34)  | 1.15 (0.49-2.66)  | 0.63        | 1.26 (0.81-1.94) |
| Multivariable* HR (95%CI)                  | 1.0           | 1.19 (0.56-2.50)  | 1.55 (0.73-3.30)  | 1.13 (0.48-2.64)  | 0.65        | 1.24 (0.79-1.93) |
| Multivariable* sHR (95% CI)                | 1.0           | 1.18 (0.56-2.49)  | 1.54 (0.71-3.36)  | 1.09 (0.46-2.61)  | 0.70        | 1.22 (0.79-1.88) |
| <b>Women</b>                               | < 147.9       | 148.0-150.9       | 151.0-154.9       | ≥ 155.0           |             |                  |
| <b>No. at risk</b>                         | 13,934        | 14,211            | 13,391            | 15,801            |             |                  |
| <b>Person-years</b>                        | 220,253       | 235,102           | 228,819           | 271,509           |             |                  |
| <b>Total aortic disease (n)</b>            | 26            | 24                | 27                | 23                |             |                  |
| Crude mortality rate per 1000 person-years | 0.12          | 0.1               | 0.12              | 0.08              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 1.10 (0.63-1.93)  | 1.79 (1.03-3.11)  | 1.57 (0.88-2.83)  | 0.05        | 1.32 (0.94-1.87) |
| Multivariable* HR (95%CI)                  | 1.0           | 1.10 (0.63-1.94)  | 1.85 (1.06-3.24)  | 1.54 (0.85-2.79)  | 0.06        | 1.33 (0.94-1.88) |
| Multivariable* sHR (95% CI)                | 1.0           | 1.10 (0.63-1.92)  | 1.87 (1.05-3.32)  | 1.53 (0.86-2.73)  | 0.06        | 1.32 (0.95-1.82) |
| <b>Total aortic aneurysm (n)</b>           | 10            | 12                | 7                 | 6                 |             |                  |
| Crude mortality rate per 1000 person-years | 0.05          | 0.05              | 0.03              | 0.02              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 1.59 (0.68-3.72)  | 1.46 (0.54-3.93)  | 1.34 (0.47-3.82)  | 0.64        | 1.22 (0.68-2.18) |
| Multivariable* HR (95%CI)                  | 1.0           | 1.61 (0.68-3.81)  | 1.50 (0.55-4.10)  | 1.26 (0.44-3.65)  | 0.71        | 1.19 (0.67-2.11) |
| Multivariable* sHR (95% CI)                | 1.0           | 1.59 (0.69-3.64)  | 1.40 (0.48-4.07)  | 1.22 (0.43-3.46)  | 0.78        | 1.15 (0.62-2.11) |
| <b>Thoracic aortic aneurysm (n)</b>        | 7             | 4                 | 4                 | 2                 |             |                  |
| Crude mortality rate per 1000 person-years | 0.03          | 0.02              | 0.02              | 0.01              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 0.75 (0.22-2.61)  | 1.12 (0.31-4.02)  | 0.59 (0.12-3.02)  | 0.65        | 0.60 (0.28-1.28) |
| Multivariable* HR (95%CI)                  | 1.0           | 0.82 (0.23-2.94)  | 1.17 (0.31-4.36)  | 0.56 (0.11-2.94)  | 0.60        | 0.64 (0.30-1.34) |
| Multivariable* sHR (95% CI)                | 1.0           | 0.83 (0.22-3.14)  | 1.21 (0.30-4.88)  | 0.56 (0.12-2.63)  | 0.58        | 0.65 (0.33-1.28) |
| <b>Abdominal aortic aneurysm (n)</b>       | 2             | 6                 | 3                 | 4                 |             |                  |
| Crude mortality rate per 1000 person-years | 0.01          | 0.03              | 0.01              | 0.01              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 4.22 (0.85-21.07) | 3.49 (0.57-21.27) | 5.22 (0.93-29.46) | 0.08        | 2.58 (1.29-5.15) |
| Multivariable* HR (95%CI)                  | 1.0           | 4.54 (0.84-24.58) | 4.19 (0.63-27.97) | 5.67 (0.90-35.77) | 0.08        | 2.64 (1.15-60.6) |
| Multivariable* sHR (95% CI)                | 1.0           | 4.17 (1.19-14.63) | 3.83 (0.79-18.54) | 5.06 (1.10-23.21) | 0.06        | 2.52 (1.30-4.88) |
| <b>Aortic dissection (n)</b>               | 16            | 12                | 20                | 17                |             |                  |
| Crude mortality rate per 1000 person-years | 0.07          | 0.05              | 0.09              | 0.06              |             |                  |
| Age- adjusted, area- stratified HR (95%CI) | 1.0           | 0.85 (0.40-1.80)  | 1.96 (1.00-3.86)  | 1.68 (0.82-3.44)  | 0.04        | 1.39 (0.91-2.13) |
| Multivariable* HR (95%CI)                  | 1.0           | 0.85 (0.40-1.81)  | 2.05 (1.03-4.05)  | 1.70 (0.82-3.50)  | 0.04        | 1.44 (0.93-2.23) |
| Multivariable* sHR (95% CI)                | 1.0           | 0.85 (0.40-1.78)  | 2.07 (1.03-4.16)  | 1.69 (0.83-3.46)  | 0.04        | 1.44 (0.99-2.09) |

CI, confidence interval; HR indicates hazard ratio; and sHR, subdistribution hazard ratio. \* Adjustment for age, body mass index, alcohol intake, cigarette smoking status, perceived mental stress, walking, sports, educational level, fresh fish intake, and employment status.

the competing risk of pre-aortic disease mortality was considered. This study is the first to find a positive sex-specific association of height with mortality from AAA and no association between height and mortality from TAA.

Research on the association between height and risk of aortic disease has been modest in previous studies. The Emerging Risk Factors Collaboration consisting of 121 prospective studies involving 1,085,949 participants, most of whom were in Europe (60%) or North America (33%), reported that a 1SD (6.5 cm) higher height was positively associated with mortality from aortic aneurysm (multivariable HR, 95% CI per 1 SD higher height=1.12, 1.05–1.20)<sup>7</sup>. Another prospective study with 18,403 British men aged 40–64 years old reported that height (per 1 cm increase) was positively associated with mortality from aortic aneurysm (multivariable HR, 95% CI per 1 cm increase in height=1.03, 1.00–1.06)<sup>8</sup>. Other prospective study with 8,361 British men aged 16–30 years old reported a non-significant association between height (per 10-cm increase) and mortality from aortic aneurysm in 8 men who died from this cause (multivariable HR, 95% CI per 10-cm increase in height=1.63, 0.55–4.84)<sup>9</sup>, which was partly due to the small number of deaths from aortic aneurysms. A prospective study involving 161,808 American women aged 50–79 years old reported that height (per 10 cm increase) was positively associated with risk of incident AAA (multivariable HR, 95% CI per 10-cm increase in height=1.50, 1.15–1.96)<sup>10</sup>. Another prospective study with 104,813 American men and women aged over 18 years old has also reported that a 1 SD (no detailed description) higher height was positively associated with risk of incident AAA (multivariable HR, 95% CI per 1 SD higher height=1.16, 1.05–1.28)<sup>11</sup>. Other prospective study with 15,792 American men and women aged 45–64 years old has also reported that height was positively associated with risk of clinical AAA events (multivariable HR, 95% CI in the highest tertile compared the lowest tertile of height=1.64, 1.16–2.31, *p* for trend=0.005)<sup>12</sup>. A prospective study of 7,682 men of Japanese ancestry in Hawaii aged 46–65 years old reported that height was positively associated with risk of incident aortic aneurysms (multivariable relative risk [RR], 95% CI per 16-cm difference in height=2.33, 1.52–3.54), but not with the risk of incident ADs (corresponding RR, 95% CI=1.08, 0.48–1.67)<sup>13</sup>. Possible reasons for our weaker association between height and aortic aneurysm than that study<sup>13</sup> included difference in the methods in measurement of height (self-reported in this present study versus actually measured in the previous study)

and difference in outcome certification (death certificates in this present study versus medical, surgical, and autopsy records in the previous study). To date, no study has examined the associations between height and the risks of three types of aortic disease (AAA, TAA, and AD).

We consider that elevated biomechanical stress on the arterial wall due to taller height could partially explain the height-aortic disease association. The final common pathway of aortic disease is that the biomechanical wall stress often exceeds the strength of the arterial wall<sup>3</sup>. Higher peak wall stress on the aorta has been established as a risk factor for aortic disease<sup>4, 5</sup>. Taller height is associated with higher peak wall stress on the aorta<sup>6</sup>, partially because taller individuals have aortas with larger diameters, which, in turn, have greater wall stress, as described by the physical law of Laplace (wall tension is equal to pressure multiplied by radius)<sup>27</sup>.

A possible explanation for this observed association between height and mortality from aortic disease, specifically AAA but not TAA, could be that the abdominal aorta is less tolerant, whereas the thoracic aorta is tolerant of aortic wall degeneration caused by the increase in peak of aortic pressure wave associated with taller height. As a premise to the difference in tolerance of aortic wall degeneration between the thoracic and abdominal aorta, the thoracic aorta is rich in elastic plate layers buffering pressure, whereas the abdominal aorta is not<sup>23, 24</sup>.

The amplitude of the aortic pressure wave has been noted to increase as the distance of pressure wave propagation increases, known as “peaking”<sup>21, 22</sup>. In the longer aorta of taller individuals, the distance where the propagation of aortic pressure wave occurs is noted to be longer, and as a result, the amplitude of the aortic pressure wave increases in the peripheral part of the aorta, which is a structurally fragile area.

Peak pressure amplification in structurally fragile abdominal aorta may denature the aortic wall, and biomechanical wall stress may subsequently exceed the mechanical strength of the arterial wall, resulting in abdominal aortic disease. These pathophysiological findings may partially explain the observed association between height and mortality from AAA, but not TAA.

The absence of the significant association between height and mortality from AD in this present study could be partly explained by modest sample size and by the fact that 67% of ADs were type A with dissection in the thoracic aorta<sup>28</sup>. Our result was similar to that observed in the previous study of Japanese-Hawaiian men<sup>13</sup> (multivariable HR, 95% CI per 10-cm difference in height=1.24, 0.79–1.93

in this present study and multivariable RR, 95% CI per 16-cm difference in height=1.08, 0.48–1.67 in the previous study). However, a larger population study will be needed to confirm this finding because of the modest sample size of both studies. The non-significant and non-linear positive trend between height and mortality from total aortic disease was probably due to the fact that AD accounted for about half of the aortic diseases in the present study.

In this present study, the positive association between height and aortic disease was more prominent among women than among men. The reasons behind the sex difference in the risk of mortality from aortic disease according to height have not been fully elucidated; however, they may be partially explained by the fact that women have higher peak aortic wall stress than men<sup>6)</sup>, which warrants further investigation. Since height is not a modifiable risk factor, it is important to control for established risk factors for aortic disease (e.g., blood pressure and smoking), especially in people with tall height.

This present study had several strengths. First, this current study had a prospective design and a long follow-up duration. Second, the JACC Study is a large, nationwide, community-based Japanese cohort, which allowed us to examine the associations between height and aortic disease type. Third, the lower distribution of height in the Japanese population than in American and English population enabled us to examine the potential impact of lower heights, which can be difficult to examine in Western countries. Our results potentially augment the current evidence on the height-aortic disease association in populations with lower height distributions, although the generalizability should be cautiously considered.

This study had several limitations. First, our data were based on self-reported height. However, a previous study demonstrated the validity of self-reported height in the Japanese population (Pearson's  $r$  for men and women between self-reported and measured height: 0.979 and 0.988, respectively)<sup>29)</sup>. Assuming that the discrepancy between measured and self-reported height is a non-differential misclassification, the real association would be greater. Second, the number of aortic disease cases among our participants was modest, although it yielded sufficient numbers to detect significant associations. Third, we ascertained aortic disease based on death certificates, as data from imaging studies or autopsies were unavailable. Although the validity of aortic disease reported on death certificates has not been fully confirmed, the high distribution of computed tomography and magnetic resonance imaging in Japan (the highest in the world)<sup>30)</sup> as well as common

postmortem imaging at large hospitals with emergency room facilities<sup>31)</sup> may contribute to the accuracy of diagnosis on the death certificate. Fourth, there might be other unmeasured confounding factors such as family history of aortic disease or socioeconomic factors.

## Conclusion

In conclusion, we have found a positive association between height and mortality from aortic disease, especially for AAA in a large, nationwide, community-based Japanese cohort. This observation potentially expands current evidence on height-aortic disease association in lower height populations such as the Asian population.

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### COI Disclosure

The authors declared no conflict of interest.

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