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Body Mass Index and Mortality from Nonrheumatic Aortic Valve Disease among Japanese Men and Women

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Aim: We aimed to examine the impact of overweight and obesity on mortality from nonrheumatic aortic valve disease.

Methods: In the Japan Collaborative Cohort Study, we analyzed data of 98,378 participants aged 40–79 years, with no history of coronary heart disease, stroke, or cancer at baseline (1988–1990) and who completed a lifestyle questionnaire including height and body weight; they were followed for mortality until the end of 2009. The Cox proportional hazards model was used to calculate the multivariable hazard ratios (HRs) with 95% confidence intervals (CIs) of nonrheumatic aortic valve disease mortality according to body mass index (BMI) after adjusting for potential confounding factors.

Results: During the median 19.2 years follow-up, 60 deaths from nonrheumatic aortic valve disease were reported. BMI was positively associated with the risk of mortality from nonrheumatic aortic valve disease; the multivariable HRs (95% CIs) were 0.90 (0.40–2.06) for persons with BMI <21 kg/m^2, 1.71 (0.81–3.58) for BMI 23–24.9 kg/m^2, 1.65 (0.69–3.94) for BMI 25–26.9 kg/m^2, and 2.83 (1.20–6.65) for BMI ≥ 27 kg/m^2 (p for trend=0.006), compared with persons with BMI 21–22.9 kg/m^2. Similar associations were observed between men and women (p for interaction=0.56). Excluding those who died during the first ten years of follow-up or a competing risk analysis with other causes of death as competing risk events did not change the association materially.

Conclusions: Overweight and obesity may be independent risk factors for nonrheumatic aortic valve disease mortality in Asian populations.

Key words: Body mass index, Aortic valve disease, Cohort study, Overweight, Obesity

Introduction

Nonrheumatic aortic valve disease is attributable to progressive calcification of the aortic valve or annulus. It results in aortic valve stenosis (AS) or aortic valve regurgitation (AR)[1, 2]. Mild to moderate nonrheumatic aortic valve disease is asymptomatic but can gradually progress to the severe stage, thereby causing heart failure, severe infection, and sudden cardiac death[3]. The mortality rate of AS over two years is more than 50% among patients with cardiac symptoms who do not undergo prompt aortic valve replacement[4].

The recent evolution of transcatheter aortic valve replacement has increased treatment options for inoperable patients and high-risk populations[5]. However, nonrheumatic aortic valve disease continues to have high mortality and morbidity, causing 102,700 (95% uncertainty interval [UI], 82,700–107,900) deaths and 1.5 million (95% UI, 1.4–1.6 million) disability-adjusted life years globally in 2017 [2]. Despite this clinical and public health importance,

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there are no medical therapies available to prevent or slow the progression of the disease. Therefore, identifying modifiable lifestyle risk factors to prevent deaths from nonrheumatic aortic valve disease is critical for reducing the disease burden.

Several European studies suggested that high BMI can be an independent risk factor for the incidence and progression of AS[6, 7]. A cohort study of 71,817 Swedish men and women with a mean follow-up of 15.3 years showed that the multivariable hazard ratios of incident AS was 1.24 (95% confidence interval [CI] 1.05–1.48) for overweight (BMI 25.0–29.9 kg/m^2) and 1.81 (95% [CI] 1.47–2.23) for obesity (BMI ≥ 30 kg/ m^2), compared with BMI 18.5–22.5 kg/m^2 [6]. Another cohort study in Northern Norway performed three repeated echocardiographic examinations for 3,243 individuals over 14 years, and a total of 132 participants developed incident AS during the follow-up[7]. They further conducted subgroup analyses for 118 out of 132 participants who developed AS to examine the risk factors for the increased progression rate of AS. Using a multivariate regression model, they confirmed an association between body weight (kg) and increased transvalvular mean gradient (mmHg) (β=0.045 [95% {CI} 0.01–0.08], p=0.015)[7].

To the best of our knowledge, no study has examined the association between BMI and the risk of nonrheumatic aortic valve disease among Asian populations, although the scientific evidence on the risk of nonrheumatic aortic valve disease is warranted considering their different anthropometry from Western cohorts[8] and their rapid population aging[9]. Therefore, the present study aimed to examine the association between BMI and nonrheumatic aortic valve disease mortality in a large long-term cohort study of Japanese men and women.

Methods

Study Design and Population

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) is a large nationwide community-based prospective study that started between 1988 and 1990 and enrolled 110,585 individuals (46,395 men and 64,190 women) aged 40–79 years, living in 45 communities across Japan. The methodology of the JACC study has been described elsewhere[10]. Briefly, 110,585 participants were asked to complete self-administered questionnaires, including demographic characteristics, medical history, lifestyle, and diet.

Of the 110,585 cohort participants, we excluded 6,805 participants (2,519 men and 4,286 women) with either missing or extreme BMI values (BMI <15 or BMI >45 kg/m^2). Furthermore, we excluded 5,402 participants (2,404 men and 2,998 women) who reported a history of coronary heart disease, stroke, or cancer at baseline. Finally, the analyses included 98,378 participants (41,472 men and 56,906 women).

Before completing the questionnaire, the participants or community representatives provided informed consent to participate in this epidemiological study under the Council for International Organizations of Medical Sciences guidelines. Each participant provided informed consent in 36 of the 45 study areas (written consent in 35 areas and oral consent in one area). In the remaining nine areas, group consent was obtained from each area leader. The ethics committees approved the study protocol of Nagoya University and Osaka University.

Assessment of Body Mass Index

We asked the participants to provide their height and weight information. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). With reference to World Health Organization (WHO) classification[11] and our previous study[12], BMI was grouped into the following five categories: <21.0, 21.0–22.9 (reference), 23.0–24.9, 25.0–26.9, and ≥ 27.0 kg/m^2. Because of the relatively low percentage of the categories of persons with BMI <18.5 (5.7%) and ≥ 30.0 (1.7%) kg/m^2, the categories of BMI <18.5 and 18.5–20.9 kg/m^2, and BMI 27.0–29.9 and ≥ 30.0 kg/m^2 were combined.

Assessment of Confounding Variables

Other demographic and lifestyle factors were derived from a self-administered questionnaire at baseline: age, sex, height, weight, past medical history (such as diabetes and hypertension), smoking and alcohol drinking status, exercise and walking habits, mental status, educational level, occupation, and eating habits.

Mortality Surveillance

A systematic review of death certificates was conducted for each area to determine the causes of death. Mortality data were sent centrally to the Ministry of Health and Welfare through the local public health center. The underlying cause of death was coded for the National Vital Statistics according to the International Classification of Diseases, 10th revision (ICD10). Follow-up terminated at the end of 1999 in four areas, at the end of 2003 in another four

areas, at the end of 2008 in two areas, and at the end of 2009 in the rest of the areas. The endpoint of death in this study was nonrheumatic aortic valve disease (I350–I359). The date of moving from the community was verified using the population registration documents. When participants moved out, they were treated as censored cases.

Statistical Analyses

Person-years of follow-up were calculated as the duration from the date of the baseline questionnaire to the date of death and emigration from the study area or the end of follow-up, whichever occurred first. Generalized linear models were used to calculate age-adjusted mean values and proportions of cardiovascular risk factors and trend testing. Age- and sex-adjusted and multivariable hazard ratios (HRs) were calculated with 95% confidence intervals (CIs) of nonrheumatic aortic valve disease mortality according to BMI after adjusting for potential confounding factors using the Cox proportional hazards model. In the multivariable analyses, we adjusted for age (continuous), sex (women or men), and history of hypertension (yes or no) in model 1. In model 2, we further adjusted for history of diabetes (yes or no), smoking status (never, ex-smoker, current smoker of 1–19, or a current smoker of ≥ 20 cigarettes per day), alcohol consumption (never drinker, ex-drinker, current drinker of 0.1–45.9, or ≥ 46.0 g ethanol per day), hours of exercise (seldom, 1–4 hours, or ≥ 5 hours per week), hours of walking (seldom, < 1 hour, or ≥ 1 hour per day), perceived mental stress (low, moderate, or high), educational level (≤ 18 or ≥ 19 years of age upon completion of education), employment status (unemployed or employed), frequency of consuming vegetables, fish, fruits, and soybean intakes (quintile). The linear trend test was performed by assigning median BMI values to each BMI category and treating it as a continuous variable in the model. We evaluated the effect modification by sex using the cross-product terms of sex and BMI.

For secondary analyses, subdistribution hazard ratios with 95% CIs were estimated to evaluate the potential impacts of competing risk bias on the association using the Fine-Gray competing risk regression models, with other causes of death as competing risk events[13]. Furthermore, we performed sensitivity analyses by excluding all participants who died during the first ten years of follow-up to account for potential bias due to reverse causality. Finally, we evaluated cause-specific mortality of AS (ICD 10 code: I350) and AR (ICD 10 code: I351). SAS version 9.4 (SAS, Inc., Cary, NC) was used for all statistical analyses.

Results

Table 1 presents the participants' sex-specific and age-adjusted baseline characteristics according to BMI. Both men and women with higher BMI were more likely to be hypertensive, diabetic, and walked less than those with lower BMI. Men with higher BMI were younger, less unemployed, and smoked less, whereas women with higher BMI were less educated and had a lower prevalence of high mental stress than those with lower BMI.

During the median 19.2 years of follow-up, a total of 60 deaths from nonrheumatic aortic valve disease were documented. In age- and sex-adjusted analyses, BMI was positively associated with mortality risk from nonrheumatic aortic valve disease **(Table 2)**. After additional adjustment for history of hypertension, the association was attenuated but remained statistically significant (Model 1). Further adjustment for other potential confounding factors slightly attenuated the association, but did not change the results materially; the multivariable HRs (95% CIs) in model 2 were 0.90 (0.40–2.06) for persons with BMI <21 kg/m^2, 1.71 (0.81–3.58) for BMI 23–24.9 kg/m^2, 1.65 (0.69–3.94) for BMI 25–26.9 kg/m^2 and 2.83 (1.20–6.65) for BMI ≥ 27 kg/m^2 (p for trend=0.006), compared with persons with BMI 21–22.9 kg/m^2. There were similar associations in men and women (p for interaction=0.56); the multivariable HRs (95% CIs) of BMI ≥ 27 kg/m^2 were 2.69 (0.76–9.44) among men and 3.21 (0.96–10.72) among women compared with persons with BMI 21–22.9 kg/m^2. **Supplemental Table 1** presents multivariable HRs (95% CIs) of covariates other than BMI for reference.

Similar associations were observed in competing risk analysis in the sensitivity analyses, with other causes of death as a competing event **(Supplemental Table 2)**. Excluding all participants who died within the first ten years of follow-up (n=8544) did not change the association materially **(Supplemental Table 3)**. The excess risk was more evident for AS than AR **(Supplemental Table 4)**.

Discussion

In this prospective cohort study of Japanese men and women aged 40–79 years, we found that persons with BMI ≥ 27.0 kg/m^2 had approximately three times the risk of mortality from nonrheumatic aortic valve disease than those with BMI 21–22.9 kg/m^2. To the best of our knowledge, this is the first study to find an association between BMI and nonrheumatic aortic valve disease mortality in an Asian population.

Table 1. Sex-specific and age-adjusted baseline characteristics of participants according to body mass index

	BMI, kg/m^2					
	<21	21–22.9	23–24.9	25–26.9	≥ 27	*P* for trend
Men						
No. of participants	11938	11876	10032	5010	2616	
Age, y	59.2	56.9	55.8	55.2	54.8	<0.001
History of hypertension, %	13.9	18.7	22.7	27.0	30.6	<0.001
History of diabetes mellitus, %	6.1	6.3	6.7	7.9	8.7	<0.001
Current smoker, %	62.0	55.1	48.9	46.2	44.2	<0.001
Current drinker, %	68.4	73.0	73.1	71.5	68.2	0.40
High mental stress, %	24.4	21.7	22.8	22.3	24.1	0.97
College or higher education, %	16.2	17.5	18.7	19.7	16.5	0.22
Unemployed, %	17.3	16.0	15.6	15.6	15.3	0.008
Walking ≥ 30min/day, %	88.3	88.8	87.2	86.1	82.8	<0.001
Exercise ≥ 1h/week, %	30.0	31.8	32.8	32.8	28.9	0.57
Vegetable intake, times/week	12.9	13.3	13.3	13.1	13.0	0.78
Fish intake, times/week	6.4	6.5	6.4	6.4	6.5	0.52
Fruits intake, times/week	6.2	6.4	6.5	6.4	6.4	0.12
Soybeans intake, times/week	4.6	4.8	4.8	4.7	4.6	0.78
Women						
No. of participants	15446	15346	13210	7535	5369	
Age, y	57.8	56.6	56.6	57.3	57.2	0.21
History of hypertension, %	14.0	19.7	24.1	29.4	36.8	<0.001
History of diabetes mellitus, %	3.1	3.9	3.9	4.2	6.0	<0.001
Current smoker, %	6.1	4.5	4.5	4.5	6.9	0.03
Current drinker, %	14.5	15.0	15.7	15.5	13.9	0.51
High mental stress, %	21.9	20.0	19.5	19.1	19.5	<0.001
College or higher education, %	11.5	11.0	9.2	9.0	7.1	<0.001
Unemployed, %	20.9	19.6	18.6	18.9	20.8	0.61
Walking ≥ 30min/day, %	90.0	89.8	89.1	89.0	86.3	<0.001
Exercise ≥ 1h/week, %	23.6	24.9	24.7	23.3	20.9	<0.001
Vegetable intake, times/week	15.1	15.5	15.6	15.5	15.3	0.09
Fish intake, times/week	6.4	6.6	6.7	6.7	6.7	<0.001
Fruits intake, times/week	8.3	8.5	8.5	8.4	8.1	<0.001
Soybeans intake, times/week	5.2	5.3	5.4	5.3	5.2	0.59

Data are mean for continuous variables and percentages for categorical variables.

Our results on the association between higher BMI and an increased risk of nonrheumatic aortic valve disease are consistent with previous studies in Western countries. In a Swedish cohort study of 71,817 Swedish men and women, BMI was positively associated with AS incidence. The multivariable HRs were 1.24 (95% [CI] 1.05–1.48) for overweight (BMI 25.0–29.9 kg/m^2) and 1.81 (95% [CI] 1.47–2.23) for obesity (BMI ≥ 30 kg/ m^2), compared with BMI 18.5–22.5 kg/m^2 [6]. Another cohort study of 3,243 Norwegian participants conducted three repeated echocardiographic examinations over the 14 years and found age-adjusted HRs of incident AS were 1.04 (95% [CI] 1.02–1.60) per 1 kg/m^2 increase in BMI[7].

More recently, a Mendelian randomization study including 108,211 individuals in the general Danish population reported that genetic predisposition to obesity was associated with an increased risk of incident AS and aortic valve replacement[14]. They also observed that the multivariable HRs of incident AS during the median 8.7 years follow-up, were 1.3 (95% [CI] 1.1–1.5) for persons with BMI 25.0–29.9 kg/m^2, 1.8 (95% [CI] 1.5–2.2) for BMI 30.0–34.9 kg/m^2 and 2.6 (95% [CI] 2.0–3.5) for BMI ≥ 35.0 kg/ m^2, compared with BMI 18.5–24.9 kg/m^2 [14]. A potential mechanism for the influence of higher BMI on mortality from nonrheumatic aortic valve disease can be primarily mediated by hypertension. Previous studies also revealed a positive association between hypertension and the risk of incidence of AS[7, 15] and

Table 2. Multivariable hazard ratios (95% confidence interval) of mortality from nonrheumatic aortic valve disease according to body mass index

	BMI, kg/m^2					
	< 21	21–22.9	23–24.9	25–26.9	≥ 27	*P* for trend
Total						
Person-years	430526	451271	389135	209851	133570	
No. of cases	12	12	17	9	10	
Mortality rate (per 10000 person-years)	0.28	0.27	0.44	0.43	0.75	
Age- and sex-adjusted HR (95% CI)	0.90 (0.40-2.00)	Ref	1.76 (0.84-3.69)	1.78 (0.75-4.22)	3.28 (1.41-7.64)	0.001
Model 1: Multivariable HR (95% CI)	0.93 (0.42-2.09)	Ref	1.74 (0.83-3.64)	1.71 (0.72-4.08)	3.06 (1.31-7.16)	0.004
Model 2: Multivariable HR (95% CI)	0.90 (0.40-2.06)	Ref	1.71 (0.81-3.58)	1.65 (0.69-3.94)	2.83 (1.20-6.65)	0.006
Men						
Person-years	179647	191826	165528	82837	43473	
No. of cases	5	7	11	4	4	
Mortality rate (per 10000 person-years)	0.28	0.36	0.66	0.48	0.92	
Age-adjusted HR (95% CI)	0.63 (0.20-1.98)	Ref	1.99 (0.77-5.13)	1.52 (0.45-5.21)	3.20 (0.93-10.95)	0.008
Model 1: Multivariable HR (95% CI)	0.66 (0.21-2.10)	Ref	1.98 (0.77-5.12)	1.47 (0.43-5.03)	3.06 (0.89-10.55)	0.01
Model 2: Multivariable HR (95% CI)	0.68 (0.21-2.15)	Ref	2.07 (0.80-5.39)	1.53 (0.44-5.29)	2.69 (0.76-9.44)	0.02
Women						
Person-years	250880	259445	223608	127014	90097	
No. of cases	7	5	6	5	6	
Mortality rate (per 10000 person-years)	0.28	0.19	0.27	0.39	0.67	
Age-adjusted HR (95% CI)	1.26 (0.40-3.99)	Ref	1.44 (0.44-4.70)	2.04 (0.59-7.06)	3.42 (1.04-11.22)	0.05
Model 1: Multivariable HR (95% CI)	1.32 (0.42-4.17)	Ref	1.41 (0.43-4.64)	1.97 (0.57-6.82)	3.18 (0.96-10.54)	0.09
Model 2: Multivariable HR (95% CI)	1.35 (0.43-4.30)	Ref	1.40 (0.42-4.60)	1.97 (0.57-6.85)	3.21 (0.96-10.72)	0.10

HR, hazard ratio; CI, confidence interval; Ref, reference.
Model 1: adjusted for age, sex and history of hypertension.
Model 2: model 1 + adjusted for history of diabetes, smoking status, alcohol consumption, hours of exercise, hours of walking, perceived mental stress, educational level, regular employment and dietary intakes of vegetable, fish, fruits and soybeans.

AR[15], and the progression of aortic valve calcification[16]. In the present study, we found that adjustment for the history of hypertension attenuated the association materially (Model 1).

Dyslipidemia is another potential mediator of the positive association between BMI and the risk of nonrheumatic aortic valve disease[17]. A cross-sectional study of 874 Japanese men reported a positive association between prevalent aortic valve calcification, low-density lipoprotein cholesterol, and low-density lipoprotein particle concentrations[18]. Although lowering lipoprotein cholesterol levels in patients with AS did not successfully control disease progression in large randomized controlled trials[19-21], recent prospective Mendelian randomization studies showed that genetic predisposition to elevated low-density lipoprotein cholesterol and lipoprotein(a) was associated with a higher risk of AS[22-25]. These results suggest that dyslipidemia can play an important role in the early stage of developing aortic valve disease, whereas hemodynamic forces such as hypertension can become more critical in disease progression once valve calcification and remodeling are established[22].

The strength of the present study is the prospective study design minimizing recall bias of the exposure assessment and sufficient sample size to find the association, despite the relatively low incidence rate of nonrheumatic aortic valve disease in Asia[2]. However, this study has several limitations. First, we used self-reported weight and height at baseline to calculate BMI, which may underestimate weight and overestimate height. However, a previous study of 1,823 Japanese men and women aged 40–68 years showed that BMI calculated by self-reported values strongly correlated with measured BMI (r=0.94), and the mean difference was small (mean ± SD = 23.3 ± 3.0 vs. 23.2 ± 2.9)[26]. Second, we used the underlying cause of death in the national death certificate as the outcome. Therefore, the mortality rate in the present study might be underestimated because clinical documentation of valvar heart disease was generally highly specific but relatively insensitive as a cause of death, compared with postmortem autopsy identification of valvar heart disease[27]. Finally, despite our efforts to adjust for potential confounding factors, we cannot rule out the effects of unmeasured factors

or residual confounding, such as changes in BMI or blood pressure over time during the long follow-up period. In particular, we did not have baseline information regarding dyslipidemia for adjustment. Further studies, including information on lipid profiles, are warranted to validate this association.

Conclusion

A high BMI was associated with an increased risk of mortality from nonrheumatic aortic valve disease. The present study suggests that obesity can be an independent risk factor for nonrheumatic aortic valve disease in the Asian population. As with other cardiovascular diseases[28, 29], maintaining an appropriate body weight can be recommended to reduce the risk of nonrheumatic aortic valve disease.

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Conflict of Interests

None.

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Supplemental Table 1. Multivariable hazard ratios (95% confidence intervals) of all covariates associated with mortality from nonrheumatic aortic valve disease

Covariates included in the analysis	Multivariable HR* (95% CI)
Age, 10 years	4.89 (3.38-7.07)
Sex, men	2.55 (1.21-5.40)
History of hypertension	
No	Ref
Yes	1.70 (0.95-3.05)
History of diabetes mellitus	
No	Ref
Yes	0.88 (0.27-2.90)
Smoking status	
Never smoker	Ref
Ex-smoker	0.75 (0.31-1.83)
Current smoker of 1–19 cigarettes per day	0.76 (0.27-2.15)
Current smoker of ≥ 20 cigarettes per day	0.92 (0.36-2.33)
Drinking status	
Never drinker	Ref
Ex-drinker	0.40 (0.05-3.10)
Current drinker of 0.1-45.9 g ethanol per day	0.73 (0.32-1.66)
Current drinker of ≥ 46.0 g ethanol per day	1.08 (0.41-2.87)
Perceived mental stress	
Low	Ref
Moderate	2.01 (0.76-5.32)
High	2.18 (0.68-6.99)
Educational level (years of age upon completion of education)	
≤ 18	Ref
≥ 19	0.56 (0.17-1.83)
Employment status	
Employed	Ref
Unemployed	0.72 (0.37-1.41)
Hours of walking	
Seldom	Ref
<1 hour per day	0.42 (0.18-1.00)
≥ 1 hour per day	0.30 (0.13-0.71)
Hours of exercise	
Seldom	Ref
1–4 hours per week	0.97 (0.45-2.08)
≥ 5 hours per week	1.24 (0.42-3.67)
Vegetable intake	
Quintile 1 (Lowest)	Ref
Quintile 2	4.00 (0.86-18.62)
Quintile 3	2.20 (0.41-11.67)
Quintile 4	3.92 (0.81-18.87)
Quintile 5 (Highest)	1.93 (0.34-10.79)
Fish intake	
Quintile 1 (Lowest)	Ref
Quintile 2	0.89 (0.25-3.09)
Quintile 3	1.53 (0.49-4.77)
Quintile 4	0.52 (0.12-2.22)
Quintile 5 (Highest)	1.03 (0.30-3.53)
Fruits intake	
Quintile 1 (Lowest)	Ref
Quintile 2	0.55 (0.16-1.93)
Quintile 3	1.43 (0.49-4.15)
Quintile 4	0.99 (0.28-3.57)
Quintile 5 (Highest)	0.83 (0.24-2.88)
Soybeans intake	
Quintile 1 (Lowest)	Ref
Quintile 2	1.32 (0.44-3.96)
Quintile 3	1.28 (0.49-3.40)
Quintile 4	0.84 (0.28-2.51)
Quintile 5 (Highest)	0.68 (0.20-2.27)

HR, hazard ratio; CI, confidence interval; Ref, reference. *Adjusted for BMI and all other covariates.

Supplemental Table 2. Multivariable hazard ratios (HRs) and subdistribution hazard ratios (SHRs) with 95% confidence intervals (CIs) of mortality from nonrheumatic aortic valve disease according to body mass index

	BMI, kg/m^2					
	<21	21–22.9	23–24.9	25–26.9	≥27	*P* for trend
Total						
Multivariable HR (95% CI)	0.90 (0.40-2.06)	Ref	1.71 (0.81-3.58)	1.65 (0.69-3.94)	2.83 (1.20-6.65)	0.006
Multivariable SHR (95% CI)	0.81 (0.36-1.81)	Ref	1.73 (0.82-3.64)	1.70 (0.72-4.00)	2.77 (1.18-6.51)	0.006
Men						
Multivariable HR (95% CI)	0.68 (0.21-2.15)	Ref	2.07 (0.80-5.39)	1.53 (0.44-5.29)	2.69 (0.76-9.44)	0.02
Multivariable SHR (95% CI)	0.57 (0.18-1.84)	Ref	2.07 (0.78-5.46)	1.58 (0.47-5.35)	2.57 (0.73-9.04)	0.02
Women						
Multivariable HR (95% CI)	1.35 (0.43-4.30)	Ref	1.40 (0.42-4.60)	1.97 (0.57-6.85)	3.21 (0.96-10.72)	0.10
Multivariable SHR (95% CI)	1.19 (0.36-3.89)	Ref	1.38 (0.42-4.55)	1.92 (0.57-6.39)	3.17 (0.96-10.46)	0.10

HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval; Ref, reference.
Multivariable HR: adjusted for age, sex, history of hypertension, history of diabetes, smoking status, alcohol consumption, hours of exercise, hours of walking, perceived mental stress, educational level, regular employment and dietary intakes of vegetable, fish, fruits and soybeans.

Supplemental Table 3. Sensitivity analyses of mortality from nonrheumatic aortic valve disease according to body mass index, excluding all participants who died during the first ten years of follow-up

	BMI, kg/m^2					
	<21	21–22.9	23–24.9	25–26.9	≥ 27	*P* for trend
Total						
Person-years	412215	438402	379391	204434	129961	
No. of cases	10	10	13	8	9	
Mortality rate (per 10000 person-years)	0.24	0.23	0.34	0.39	0.69	
Age- and sex-adjusted HR (95% CI)	0.93 (0.39-2.24)	Ref	1.59 (0.70-3.62)	1.86 (0.73-4.71)	3.44 (1.39-8.52)	0.003
Model 1: Multivariable HR (95% CI)	0.96 (0.40-2.32)	Ref	1.58 (0.69-3.60)	1.81 (0.71-4.59)	3.27 (1.31-8.15)	0.006
Model 2: Multivariable HR (95% CI)	0.93 (0.39-2.26)	Ref	1.59 (0.69-3.63)	1.74 (0.68-4.43)	3.01 (1.20-7.56)	0.009
Men						
Person-years	168022	183540	159714	79877	41849	
No. of cases	5	5	8	3	4	
Mortality rate (per 10000 person-years)	0.30	0.27	0.50	0.38	0.96	
Age- and sex-adjusted HR (95% CI)	0.91 (0.26-3.16)	Ref	1.98 (0.65-6.04)	1.55 (0.37-6.49)	4.39 (1.17-16.37)	0.02
Model 1: Multivariable HR (95% CI)	0.96 (0.28-3.35)	Ref	2.00 (0.65-6.11)	1.52 (0.36-6.38)	4.38 (1.16-16.50)	0.03
Model 2: Multivariable HR (95% CI)	0.94 (0.27-3.28)	Ref	2.13 (0.69-6.61)	1.53 (0.36-6.52)	4.13 (1.07-15.96)	0.03
Women						
Person-years	244193	254862	219677	124557	88111	
No. of cases	5	5	5	5	5	
Mortality rate (per 10000 person-years)	0.20	0.20	0.23	0.40	0.57	
Age- and sex-adjusted HR (95% CI)	0.94 (0.27-3.24)	Ref	1.18 (0.34-4.08)	2.02 (0.59-6.99)	2.81 (0.82-9.72)	0.05
Model 1: Multivariable HR (95% CI)	0.97 (0.28-3.36)	Ref	1.17 (0.34-4.03)	1.96 (0.57-6.79)	2.64 (0.76-9.23)	0.07
Model 2: Multivariable HR (95% CI)	0.97 (0.28-3.39)	Ref	1.18 (0.34-4.11)	1.97 (0.57-6.86)	2.63 (0.75-9.31)	0.08

HR, hazard ratio; CI, confidence interval; Ref, reference.
Multivariable HR:
Model 1: adjusted for age, sex and history of hypertension.
Model 2: model 1 + adjusted for history of diabetes, smoking status, alcohol consumption, hours of exercise, hours of walking, perceived mental stress, educational level, regular employment and dietary intakes of vegetable, fish, fruits and soybeans.

Supplemental Table 4. Multivariable hazard ratios (95% confidence interval) of mortality from aortic valve stenosis and aortic valve regurgitation according to body mass index

	BMI, kg/m^2					
	<21	21–22.9	23–24.9	25–26.9	≥ 27	*P* for trend
Aortic valve stenosis						
Person-years	430526	451271	389135	209851	133570	
No. of cases	3	6	9	5	5	
Mortality rate (per 10000 person-years)	0.07	0.13	0.23	0.24	0.37	
Age- and sex-adjusted HR (95% CI)	0.44 (0.11-1.77)	Ref	1.89 (0.67-5.31)	1.96 (0.60-6.45)	3.19 (0.97-10.54)	0.002
Model 1: Multivariable HR (95% CI)	0.47 (0.12-1.89)	Ref	1.86 (0.66-5.22)	1.87 (0.57-6.16)	2.89 (0.87-9.64)	0.005
Model 2: Multivariable HR (95% CI)	0.43 (0.11-1.75)	Ref	1.82 (0.64-5.16)	1.81 (0.55-5.98)	2.47 (0.73-8.38)	0.009
Aortic valve regurgitation						
No. of cases	6	6	5	3	4	
Mortality rate (per 10000 person-years)	0.14	0.13	0.13	0.14	0.30	
Age- and sex-adjusted HR (95% CI)	0.87 (0.28-2.70)	Ref	1.04 (0.32-3.40)	1.22 (0.31-4.91)	2.88 (0.81-10.30)	0.12
Model 1: Multivariable HR (95% CI)	0.90 (0.29-2.80)	Ref	1.03 (0.31-3.38)	1.19 (0.30-4.79)	2.75 (0.76-9.91)	0.16
Model 2: Multivariable HR (95% CI)	0.95 (0.30-2.97)	Ref	1.06 (0.32-3.48)	1.26 (0.31-5.09)	2.58 (0.70-9.49)	0.19

HR, hazard ratio; CI, confidence interval; Ref, reference.
The International Classification of Diseases, 10th revision code for aortic valve stenosis and aortic valve regurgitation were I350 and I351, respectively.
Multivariable HR:
Model 1: adjusted for age, sex and history of hypertension.
Model 2: model 1 + adjusted for history of diabetes, smoking status, alcohol consumption, hours of exercise, hours of walking, perceived mental stress, educational level, regular employment and dietary intakes of vegetable, fish, fruits and soybeans.