Overall and abdominal obesity and incident aortic valve stenosis: two prospective cohort studies

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Aims

The aim of this study was to examine the association of overall and abdominal obesity with aortic valve stenosis (AVS) incidence in two prospective cohorts.

Methods and results

We used data from the Cohort of Swedish Men and the Swedish Mammography Cohort, involving 71,817 men and women who were free of cardiovascular disease and had reported their anthropometric measures in 1997. Aortic valve stenosis cases were ascertained through linkage with nationwide registers on hospitalization and causes of death. Data were analysed using Cox proportional hazards regression. During a mean follow-up of 15.3 years, 1,297 incident AVS cases (771 in men; 526 in women) were ascertained. Both overall and abdominal obesity, measured as body mass index (BMI) and waist circumference, respectively, was associated with AVS incidence, with similar associations in men and women. Compared with BMI 18.5–22.5 kg/m², the multivariable hazard ratios were 1.24 (95% confidence interval [CI] 1.05–1.48) for overweight (BMI 25.0–29.9 kg/m²) and 1.81 (95% CI 1.47–2.23) for obesity (BMI ≥30 kg/m²). The hazard ratio for substantially increased waist circumference (men: ≥102 cm; women: ≥88 cm) compared with normal waist circumference (men: <94 cm; women: <80 cm) was 1.30 (95% CI 1.12–1.51). The proportion of AVS cases estimated to be attributed to overweight and obesity combined (BMI ≥25 kg/m²) was 10.8% (95% CI 5.2–16.4%).

Conclusion

These findings indicate that obesity is associated with an increased risk of AVS and that a large proportion of the cases may be prevented if the population maintained a healthy BMI.

Keywords

Aortic valve stenosis • Body mass index • Obesity • Prospective studies • waist circumference

Introduction

Aortic valve stenosis (AVS) is common, with an estimated prevalence of 2–4% in individuals 65–79 years of age,¹,² and almost 10% in those over age 80 years.³ The only treatments for AVS are either valve replacement surgery or transcatheter aortic valve implantation. Because no medical therapy is available and aortic valve replacement is related to a non-negligible risk for complications and death,³ identification of modifiable risk factors for AVS is highly desirable. The pathogenesis and risk factors for AVS are incompletely understood, but older age increases the risk,³ and available evidence indicates possible links with atherosclerotic risk factors,³ including hypertension, dyslipidaemia,²,⁵ and diabetes.³,⁶

Obesity, in particular the accumulation of visceral adiposity, is associated with metabolic disturbances leading to hypertension, dyslipidaemia and atherosclerosis.²,³ While the adverse consequences of excess adiposity on public health are widely accepted, the role of obesity in the development of AVS has remained controversial. In an initial study, body mass index (BMI), a measure of overall obesity, was inversely associated with the prevalence of aortic valve
calciﬁcation\textsuperscript{14} and an obesity paradox was suggested to apply to AVS.\textsuperscript{15} However, other small cross-sectional studies showed either no signiﬁcant association\textsuperscript{16} or positive associations\textsuperscript{17–19} between BMI and aortic valve calciﬁcation or AVS. The few available prospective studies of BMI in relation to AVS incidence were limited by a small sample size and limited number of AVS cases, ranging from 69 to 132.\textsuperscript{5,6}

The purpose of this study was to utilize data from two large population-based prospective cohorts of Swedish adults to examine the associations between overall obesity (reﬂected by BMI), and abdominal adiposity (based on waist circumference \([WC]\)) and incidence of AVS. Furthermore, we estimated the potentially modiﬁable burden of incident AVS due to obesity.

### Methods

#### Study population

We utilized two population-based prospective studies; the Cohort of Swedish Men, a cohort of 48 850 Swedish men aged 45–79 at enrolment in the late autumn of 1997, and the Swedish Mammography Cohort, a cohort of 39 227 Swedish women aged 49–83 years in 1997. Each participant completed a questionnaire on anthropometrics, lifestyle characteristics, and other potential risk factors for chronic diseases in the late autumn of 1997. For the present analysis, we excluded participants with an incorrect or a missing personal identiﬁcation number \((n = 540),\) those who died \((n = 811)\) before 1 January 1998, those with a prior diagnosis of cancer \((n = 4403)\) or cardiovascular disease \((AVS,\) ischaemic heart disease, heart failure, or ischaemic stroke; \(n = 7796))\) because they may have lost weight after the diagnosis, and those who were underweight \((BMI <18.5 \text{ kg/m}^2)\) or had missing data on BMI. Individuals with BMI 18.5–22.4 \text{ kg/m}^2 or normal WC were deﬁned as lean. \(87 \text{ cm}\) for men and >\(88 \text{ cm}\) for women. Individuals with BMI 22.5–24.9, 25.0–27.4, 27.5–29.9, and >\(30.0 \text{ kg/m}^2\) were used for categorization of abdominal adiposity based on WC.\textsuperscript{21} The categories with BMI \((\text{kg/m}^2)\) corresponding to 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, and >\(30.0 \text{ kg/m}^2\) were combined into normal or increased WC and substantially increased WC.

Assessment of obesity and covariates

Through the self-administered questionnaire administered in the autumn of 1997, participants reported their height at age 20 years, current body weight and WC, highest educational level, smoking status and history, alcohol consumption, physical activity, aspirin use, and history of diabetes, hypertension, and hypercholesterolemia. Diabetes was deﬁned as a self-reported diagnosis or a diagnosis in the Swedish National Patient or Diabetes Registers. We calculated BMI from self-reported weight \((\text{kg})\) divided by the square of height \((\text{m})\). High validity has been observed for self-reported weight \((r = 0.9)\) and height \((r = 0.9)\) compared with actual measurement in Swedish adults.\textsuperscript{20} We grouped participants into ﬁve categories with BMI \((\text{kg/m}^2)\) corresponding to 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, and >\(30.0 \text{ kg/m}^2\). World Health Organization classiﬁcation was used for categorization of abdominal adiposity based on WC.\textsuperscript{21} The categories for normal, increased, and substantially increased WC were respectively <\(94 \text{ cm}\), 94–101 cm, and >\(102 \text{ cm}\) for men and <\(80 \text{ cm}\), 80–87 cm, and >\(88 \text{ cm}\) for women. Individuals with BMI 18.5–22.4 \text{ kg/m}^2 or normal WC were deﬁned as lean.

### Ascertainment of aortic valve stenosis cases and follow-up

Aortic valve stenosis cases were identiﬁed by computerized record linkage of participants, using the personal identiﬁcation number assigned to each Swedish resident, with the Swedish National Patient Register. This register has nearly 100% complete coverage of hospital-based inpatient care.\textsuperscript{22} Since 2001, the register also includes outpatient physician visits from public and private care providers.\textsuperscript{22} Deaths from AVS and other causes were ascertained by linkage with the Swedish Cause of Death Register. The primary outcome for the present analyses was AVS, deﬁned according to the International Classiﬁcation of Diseases 10th revision codes I35.0 and I35.2. A secondary outcome was AVS with aortic valve replacement, deﬁned according to surgical and interventional cardiology procedures in the National Patient Register. Participants were followed up from 1 January 1998 until the date of diagnosis of AVS, date of death, or end of follow-up (i.e. 31 December 2014), whichever came ﬁrst.

### Statistical analysis

Hazard ratios \((HR)\) and 95% conﬁdence intervals \((CI)\) of AVS by exposure categories were estimated using Cox proportional hazards regression models with age as the underlying time scale. Analyses of men and women combined were controlled for sex as a stratum variable. All multivariable models were further adjusted for educational level (less than high school, high school, or university), smoking status and history (never, former <\(10 \text{ pack-years}\), former \(\geq 10 \text{ pack-years}\), current \(<10 \text{ pack-years}\), current \(\geq 20 \text{ pack-years}\), and dichotomous for diabetes, hypertension, and hypercholesterolemia. Additional adjustment for physical activity (walking/bicycling and exercise), alcohol consumption, and aspirin use did not change the results and therefore these variables were not included in the main multivariable model. The proportional hazards assumption was tested using Schoenfeld residuals, and was found to be satisﬁed.

Tests for trend across categories were conducted by modelling the median value for each category as a continuous variable. In addition to the categorical analyses, we modelled BMI as a continuous variable \((\text{per 5 kg/m}^2 \text{ increment})\). To avoid any potential inﬂuence of extreme values in this analysis, individuals with a BMI above the 99th percentile were omitted. Tests for interaction by sex were conducted using a likelihood ratio test that compared models with and without interaction terms.

We performed several sensitivity analyses to evaluate the robustness of the results. First, we repeated the analysis with death as a competing event, using the competing risk model \(\text{(proportional sub-hazard model)\} \) proposed by Fine and Gray.\textsuperscript{23} We also examined the impact of excluding either the ﬁrst 3 years of follow-up \((\text{to minimize potential reverse causation})\) or individuals with a history of diabetes, hypertension, or hypercholesterolemia. Additionally, we repeated the main analysis with AVS requiring aortic valve replacement as the outcome. In a post hoc analysis, we examined the joint association of BMI and WC in relation to AVS risk. In this analysis, the BMI categories were collapsed into three categories representing lean/normal BMI, overweight and obesity and the WC categories were combined into normal or increased WC and substantially increased WC.

Assuming a causal association between adiposity and AVS, we estimated the percentage of AVS cases that could potentially be prevented if all individuals maintained a healthy BMI \((18.5–24.9 \text{ kg/m}^2)\). The following formula was used calculate the population-attributable risk \((\text{PAR})\): \(P(\text{HR} - 1)/(1 + p(\text{HR} - 1))\), where \(p\) is the prevalence of exposure \((\text{BMI} \geq 25 \text{ kg/m}^2)\) in the population and \(HR\) is the hazard ratio for exposed \((\text{BMI} \geq 25 \text{ kg/m}^2)\) versus unexposed \((\text{BMI} < 25 \text{ kg/m}^2)\) individuals. Similarly, we estimated PAR for obesity \((\text{BMI} \geq 30 \text{ kg/m}^2)\) and substantially increased WC \((\geq 102 \text{ cm for men and } \geq 88 \text{ cm for women})\).

All statistical tests were two-sided, and \(P < 0.05\) was considered statistically signiﬁcant. The statistical analyses were performed using SAS \((\text{version 9.4, SAS Institute, Cary, NC})\) and Stata \((\text{version 14.2, StataCorp, Texas, USA})\).
Results

During a mean follow-up of 15.3 years (1 096 876 person-years), 1297 incident cases of AVS (771 in men and 526 in women) were ascertained. The incidence rate was 13 per 10 000 person-years in men and 10 per 10 000 person-years in women. Mean (± standard deviation) BMI was 25.8 (± 3.3) kg/m² in men and 25.1 (± 3.8) kg/m² in women. Compared with lean men and women, obese (BMI >_30 kg/m²) individuals were less likely to have a post-secondary education and to be current smokers, but were more likely to have a history of diabetes, hypertension, or hypercholesterolemia (Table 1).

Both BMI and WC were positively associated with incidence of AVS (Table 2) and there were no interactions by sex (P-interaction = 0.97 for BMI and P-interaction = 0.60 for WC). Compared with lean individuals, the multivariable HR for those with BMI >_30 kg/m² was 1.81 (95% CI 1.47–2.23). Further adjustment for physical activity = 0.97 for BMI and P-interaction = 0.60 for WC). Compared with lean individuals, the multivariable HR for those with BMI >_30 kg/m² was 1.81 (95% CI 1.47–2.23). Further adjustment for physical activity, alcohol consumption, and aspirin use yielded similar results (HR 1.80; 95% CI 1.46–2.22). The multivariable HR of AVS for overweight (BMI 25.0–29.9 kg/m²; combining categories 25.0–27.4 and 27.5–29.9 kg/m²) was 1.24 (95% CI 1.05–1.48). The multivariable HRs of AVS per 5-kg/m² increment of BMI was 1.28 (95% CI 1.17–1.39) in men and women combined, 1.31 (95% CI 1.17–1.48) in men, and 1.24 (95% CI 1.10–1.40) in women. For WC, the multivariable HR for substantially increased versus normal WC was 1.30 (95% CI 1.12–1.51). Results for BMI and WC were consistent in sensitivity analyses, including a competing risk analysis with death as a competing event, and in separate analyses excluding either the first 3 years of follow-up or individuals with a history of diabetes, hypertension, or hypercholesterolemia (see Supplementary material online, Table S1).

About one third (n = 413) of AVS patients had undergone aortic valve replacement. Both BMI and WC were positively associated with risk of AVS requiring aortic valve replacement; the multivariable HRs were 2.03 (95% CI 1.35–3.05) for BMI >_30 vs. 18.5–22.4 kg/m² and 1.60 (95% CI 1.24–2.08) for WC (substantially increased vs. normal) (Figure 1).

In a post hoc analysis, we examined the joint association of BMI and WC with AVS risk (see Supplementary material online, Table S2). This analysis revealed that individuals with substantially increased WC and BMI 25.0–29.9 kg/m² (overweight) or BMI >_30 kg/m² (obese) had an increased risk of AVS compared with lean individuals. BMI >_30 kg/m² was also positively associated with AVS risk in individuals with normal or increased WC but this estimate was not statistically significant, possibly because of small number of cases in this category.

The estimated proportion of AVS cases attributed to overweight and obesity combined (BMI >_25 kg/m²: 50.3% of the study population) was 10.8% (95% CI 5.2–16.4%) and that for obesity alone (BMI >_30 kg/m²: 10.1% of the population) was 5.3% (95% CI 3.2–7.5%). The proportion of AVS cases attributed to substantially increased WC (>_102 cm for men and >_88 cm for women; 28.1% of the population) was 7.8% (95% CI 4.0–11.9%).

Discussion

In this large prospective study, we observed a dose-response relationship between BMI and risk of AVS. Individuals with BMI >_30 kg/m² had an approximately 80% increased risk of AVS compared with lean individuals. Abdominal obesity, based on WC, was associated

### Table 1 Baseline characteristics according to categories of body mass index and waist circumference

| Characteristicsa | Body mass index, kg/m² | Waist circumferenceb |
|------------------|------------------------|----------------------|
|                  | 18.5–22.4  | 22.5–24.9  | 25.0–27.4  | 27.5–29.9  | ≥30.0  | Normal  | Increased  | Substantially increased  |
| Men (n = 38 180) |                       |                      |             |               |    |              |                      |
| Number of men    | 5269   | 11 728  | 11 702  | 5803  | 3678  | 13 278  | 10 203  | 7695  |
| Age, years (SD)  | 59.2 (10.1) | 59.1 (9.6) | 59.0 (9.3) | 59.2 (9.1) | 58.7 (8.8) | 58.4 (9.4) | 59.6 (9.5) | 60.6 (9.4) |
| Post-secondary education | 23.9  | 20.0  | 16.5  | 13.5  | 12.0  | 19.9  | 16.9  | 14.6  |
| Current smoker   | 28.4  | 25.1  | 23.9  | 23.1  | 24.6  | 24.8  | 22.0  | 23.8  |
| Diabetes         | 2.8   | 3.8   | 4.8   | 7.3   | 12.5  | 3.5   | 4.5   | 8.8   |
| Hypertension     | 12.0  | 15.3  | 22.8  | 28.5  | 38.7  | 14.5  | 21.7  | 32.4  |
| Hypercholesterolemia | 9.0  | 11.4  | 14.1  | 16.0  | 17.5  | 11.1  | 14.1  | 15.9  |
| Women (n = 33 637) | 8787  | 9921  | 7434  | 3935  | 3560  | 10 321  | 9076  | 9036  |
| Age, years (SD)  | 60.2 (9.3) | 61.0 (9.0) | 61.9 (9.0) | 62.4 (8.9) | 61.6 (8.4) | 59.5 (8.6) | 61.8 (9.1) | 63.1 (9.0) |
| Post-secondary education | 25.1  | 20.4  | 17.0  | 15.1  | 13.4  | 23.2  | 19.1  | 15.2  |
| Current smoker   | 27.9  | 23.7  | 21.5  | 20.4  | 19.0  | 24.5  | 21.8  | 21.5  |
| Diabetes         | 1.7   | 2.6   | 3.8   | 5.9   | 9.5   | 1.5   | 2.5   | 6.5   |
| Hypertension     | 13.4  | 16.7  | 21.6  | 27.6  | 35.5  | 13.9  | 18.1  | 28.9  |
| Hypercholesterolemia | 6.5  | 7.4   | 8.4   | 8.8   | 8.7   | 6.5   | 7.8   | 9.4   |

aAge-standardized to the age distribution of the study population at baseline. All values, except age, are percentages.
bThe categories for normal, increased, and substantially increased waist circumference (cm) were respectively <94, 94–101, and ≥102 for men and <80, 80–87, and ≥88 for women.
Overall and abdominal obesity and incident aortic valve stenosis

Hazard ratios of aortic valve stenosis by body mass index and waist circumference in the Cohort of Swedish Men and the Swedish Mammography Cohort, 1998–2014

| BMI (kg/m²) | Men and women | Men | Women |
|-------------|----------------|-----|-------|
| 18.5–22.4   | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 22.5–24.9   | 0.97–1.39 | 0.95–1.36 | 0.90–1.51 | 0.86–1.44 |
| 25.0–27.4   | 1.06–1.53 | 0.99–1.43 | 0.97–1.63 | 0.86–1.47 |
| 27.5–29.9   | 1.22–1.82 | 1.09–1.64 | 1.07–1.88 | 0.93–1.71 |
| ≥30.0      | 1.72–2.57 | 1.47–2.23 | 1.39–2.51 | 1.32–2.38 |

P for trend <0.0001

Waist circumference

| Men | Women |
|-----|-------|
| Normal | 1.00 (reference) | 1.00 (reference) |
| Increased | 0.90–1.21 | 0.86–1.16 |
| Substantially increased | 1.22–1.60 | 1.14–1.66 |

P for trend <0.0001

The hazard ratios were adjusted for age (time-scale), sex, education (less than high school, high school, or university), smoking status and history (never, past <10 pack-years, current <10 pack-years, current 10–19 pack-years, or current >20 pack-years), and history of diabetes, hypertension, and hypercholesterolemia.

The number of cases in the waist circumference analysis does not sum up to the total number owing to missing data.

Table 2

*The categories for normal, increased, and substantially increased waist circumference (cm) were respectively <94 cm and 80–87 cm and >88 cm for women.

**The median BMI in this category was 31.7 kg/m² for men and 32.0 kg/m² for women.

Figure 1

Hazard ratios of aortic valve stenosis requiring aortic valve replacement by body mass index and waist circumference. The reference group for BMI was 18.5–22.4 kg/m². For waist circumference, the reference group was <94 cm for men and <80 cm for women; increased and substantially increased waist circumference were respectively 94–101 cm and ≥102 cm for men and 80–87 cm and ≥88 cm for women. The hazard ratios were adjusted for age (time-scale), sex, education (less than high school, high school, or university), smoking status and history (never, past <10 pack-years, past ≥10 pack-years, current <10 pack-years, current 10–19 pack-years, or current >20 pack-years), and diabetes, hypertension, and hypercholesterolemia.

with a 30% higher risk of AVS in individuals with substantially increased WC. The associations of overall and abdominal obesity with AVS risk persisted when studying only end-stage disease defined as valve replacement, further reinforcing the importance of obesity for the outcome of AVS. Assuming a causal association, our findings indicated that over 10% of AVS cases could be prevented if the entire population maintained a BMI of less than 25 kg/m².

Small cross-sectional studies of BMI in relation to AVS and/or aortic valve calcification have provided contradictory findings, with inverse, neutral, and positive associations reported. Obesity has also been reported not to affect AVS progression, and to improve outcome in AVS patients. A prospective study, including 1323 young adults, found a positive association between BMI and aortic valve calcification, with an odds ratio of 1.21 (95% CI 1.05–1.40) per 1 SD increase in BMI. Our results for BMI confirm and extend the results from previous smaller prospective studies on AVS risk. In a random sample of 5079 adults participating in the Malmö Diet and Cancer Study, including 69 cases of AVS diagnosed during up to 20 years of follow-up, the multivariable HR of AVS per 1 SD increment of BMI was 1.28 (95% CI 1.02–1.60). This Tromsø Study of 3243 Norwegian adults, including 132 AVS cases diagnosed during 14 years of follow-up, showed age-adjusted HRs for AVS of 1.04 (95% CI 1.02–1.60) per 1 kg/m² increase in BMI (corresponding to an HR of 1.22 per 5 kg/m²) and 1.02 (95% CI 1.01–1.04) per 1 cm increase in WC.

The increased risk of AVS with increasing adiposity may, at least partly, be mediated by higher blood pressure and increased levels of atherogenic lipids. Previous data indicate that obesity is associated with hypertension and dyslipidemia. Prospective studies have reported positive associations of hypertension and levels of low-

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density lipoprotein cholesterol and lipoprotein(a) with AVS risk. Moreover, genetically predicted higher levels of low-density lipoprotein cholesterol and lipoprotein(a) have been observed to be positively associated with AVS. Obesity, particularly excess visceral adiposity, is associated with an inflammatory state, but whether inflammation contributes to the development of AVS remains unclear. In the current study, the associations of BMI and WC with AVS persisted when we restricted the analysis to participants without a history of diabetes, hypertension, and hypercholesterolemia. This suggests that obesity is not entirely reflecting the metabolic syndrome. Our post hoc analysis indicated that overweight, especially obese individuals with substantially increased WC had the highest risk of AVS, suggesting that the increased risk of AVS associated with overall obesity may be enhanced by an abdominal body fat distribution. Future studies assessing the simultaneous measurements of fasting triglycerides and WC, which may be used as screening tools to identify individuals characterized by the atherogenic metabolic triad, in relation to AVS risk are warranted.

Major strengths of this study include the prospective design, large sample size, the large number of incident AVS cases, and the objective ascertainment of cases through linkage with nationwide population-based registers. A further strength is that we were able to examine the association between obesity and end-stage disease of AVS defined as valve replacement. This has, to our knowledge, not been investigated previously. This study also has some limitations, including the use of a single questionnaire to assess BMI and WC, which likely introduced some degree of measurement error in the exposure assessment. However, because of the prospective design, any misclassification is most likely non-differential and would tend to attenuate the true association. Another limitation is the observational design. Despite adjustment for major potential confounders, we cannot rule out the possibility that the observed association between obesity and AVS may be confounded by other AVS risk factors. Given the strong dose-response relationship between BMI and risk of AVS, any unadjusted risk factor needs to be strongly related to an increased risk of AVS to completely explain the observed association. Reverse causation is another bias that could influence the results in observational studies. In this study, the positive association between obesity and AVS remained after excluding the first 3 years of follow-up, indicating that the observed association is unlikely due to reverse causation. Another potential limitation is that despite high validity of the diagnoses in the Swedish National Patient Register, the incidence of AVS may be somewhat underestimated and the generalizability of our findings to individuals not seeking specialist care is hence unknown. Finally, the observational design of the present study means that no causality can be definitely attributed and whether weight loss will decrease the risk of AVS remains to be established.

This study indicates that obesity may be an important risk factor for AVS and may explain a relatively large proportion of the cases. Mendelian randomization studies, using genetic variants associated with adiposity as instrumental variables, may shed further light on the causality of the association between obesity and AVS.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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