ESC European Society of Cardiology

European Heart Journal (2017) **38**, 2192–2197
doi:10.1093/eurheartj/ehx140

CLINICAL RESEARCH
Valvular heart disease

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

Susanna C. Larsson[1]*, Alicja Wolk[1], Niclas Håkansson[1], and Magnus Bäck[2,3]

[1]Unit of Nutritional Epidemiology, Institute of Environmental Medicine, Nobels väg 13 Karolinska Institutet, SE-17177 Stockholm, Sweden; [2] Department of Medicine, Karolinska Institutet, Centre for Molecular Medicine, SE-17176 Stockholm, Sweden; and [3]Department of Cardiology, Karolinska University Hospital, SE-17176 Stockholm, Sweden

Received 30 November 2016; revised 23 January 2017; editorial decision 2 March 2017; accepted 2 March 2017; online publish-ahead-of-print 11 April 2017

See page 2198 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx219)

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, 1297 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/m^2, the multivariable hazard ratios were 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). 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/m^2) 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.[2] 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[4] and available evidence indicates possible links with atherosclerotic risk factors,[4] including hypertension,[1,5,6] dyslipidemia,[7–11] and diabetes.[5,6]

Obesity, in particular the accumulation of visceral adiposity, is associated with metabolic disturbances leading to hypertension, dyslipidaemia and atherosclerosis.[12,13] 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

* Corresponding author. Tel: +46 8 52486059, Fax: +46 8 304571, Email: susanna.larsson@ki.se

calcification[14] and an obesity paradox was suggested to apply to AVS.[15] However, other small cross-sectional studies showed either no significant association[16] or positive associations[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.[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 ($n = 81$) 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 kg/m^2) or had missing data on BMI ($n = 3440$). After exclusions, 71 817 individuals (38 180 men and 33 637 women) remained for analysis. The analyses of WC further excluded participants who did not report their WC ($n = 12\,208$), leaving 59 609 individuals for the WC analyses. The Regional Ethical Review Board at Karolinska Institutet in Stockholm, Sweden, approved the study.

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 (in kg) divided by the square of height (in 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.[20] We grouped participants into five categories with BMI (kg/m^2) corresponding to 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0. World Health Organization classification was used for categorization of abdominal adiposity based on WC.[21] The categories for normal, increased, and substantially increased WC were respectively <94 cm, 94–101 cm, and ≥102 cm for men and <80 cm, 80–87 cm, and ≥88 cm for women. Individuals with BMI 18.5–22.4 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.[22] Since 2001, the register also includes outpatient physician visits from public and private care providers.[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 pack-years, former ≥10 pack-years, current <10-pack-years, current 10–19 pack-years, or current ≥20 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 (per 5 kg/m^2 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 (proportional sub-hazard model) proposed by Fine and Gray.[23] We also examined the impact of excluding either the first 3 years of follow-up (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 kg/m^2). The following formula was used calculate the population-attributable risk (PAR): $p\,(HR-1)/(1+p\,(HR-1))$, where p is the prevalence of exposure (BMI ≥25 kg/m^2) in the population and HR is the hazard ratio for exposed (BMI ≥25 kg/m^2) versus unexposed (BMI <25 kg/m^2) individuals. Similarly, we estimated PAR for obesity (BMI ≥30 kg/m^2) and substantially increased WC (≥102 cm for men and ≥88 cm for women).

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. The statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC) and Stata (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/m^2 in men and 25.1 (± 3.8) kg/m^2 in women. Compared with lean men and women, obese (BMI ≥30 kg/m^2 or substantially increased WC) 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/m^2 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/m^2; combining categories 25.0–27.4 and 27.5–29.9 kg/m^2) was 1.24 (95% CI 1.05–1.48). The multivariable HRs of AVS per 5-kg/m^2 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/m^2) 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/m^2 (overweight) or BMI ≥30 kg/m^2 (obese) had an increased risk of AVS compared with lean individuals. BMI ≥30 kg/m^2 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/m^2; 50.3% of the study population) was 10.8% (95% CI 5.2–16.4%) and that for obesity alone (BMI ≥30 kg/m^2; 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/m^2 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

Characteristics[a]	Body mass index, kg/m^2					Waist circumference[b]		
	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)								
Number of women	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

[a]Age-standardized to the age distribution of the study population at baseline. All values, except age, are percentages.
[b]The 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.

Table 2 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

	Men and women				Men	Women
	Cases[a]	Person-years	Age- and sex-adjusted HR (95% CI)	Multivariable HR (95% CI)[b]	Multivariable HR (95% CI)[b]	Multivariable HR (95% CI)[b]
BMI (kg/m^2)						
18.5–22.4	178	214 801	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
22.5–24.9	353	332 244	1.16 (0.97–1.39)	1.13 (0.95–1.36)	1.16 (0.90–1.51)	1.12 (0.86–1.44)
25.0–27.4	355	293 278	1.27 (1.06–1.53)	1.19 (0.99–1.43)	1.26 (0.97–1.63)	1.13 (0.86–1.47)
27.5–29.9	211	147 721	1.49 (1.22–1.82)	1.34 (1.09–1.64)	1.41 (1.07–1.88)	1.26 (0.93–1.71)
≥30.0[c]	200	108 832	2.10 (1.72–2.57)	1.81 (1.47–2.23)	1.87 (1.39–2.51)	1.77 (1.32–2.38)
P for trend			<0.0001	<0.0001	<0.0001	0.0001
Waist circumference[d]						
Normal	350	367 296	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Increased	336	295 818	1.04 (0.90–1.21)	1.00 (0.86–1.16)	0.98 (0.81–1.19)	1.02 (0.80–1.30)
Substantially increased	418	249 037	1.47 (1.27–1.69)	1.30 (1.12–1.51)	1.38 (1.14–1.66)	1.21 (0.96–1.53)
P for trend			<0.0001	0.0003	0.001	0.07

[a]The number of cases in the waist circumference analysis does not sum up to the total number owing to missing data.
[b]Adjusted for age (time-scale in the Cox model), 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 history of diabetes, hypertension, and hypercholesterolemia.
[c]The median BMI in this category was 31.7 kg/m^2 for men and 32.0 kg/m^2 for women.
[d]The categories for normal, increased, and substantially increased waist circumference (cm) were respectively <94, 94–101, and ≥102 (median 108) for men and <80, 80–87, and ≥88 (median 96) for women.

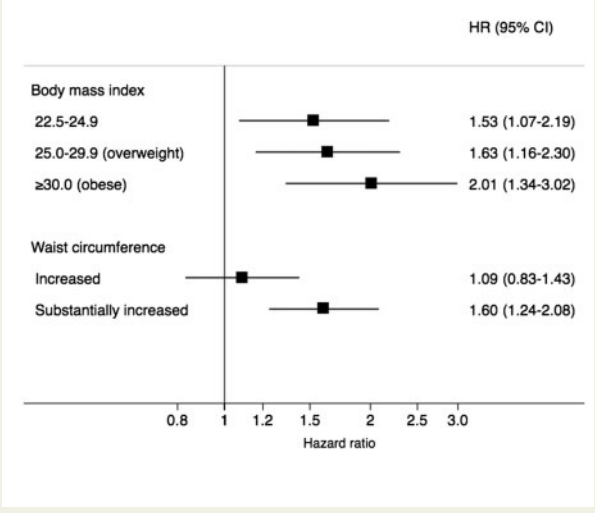

Figure 1 Hazard ratios of aortic valve stenosis requiring aortic valve replacement by body mass index and waist circumference. The reference group for BMI was 18.5–22.4 kg/m^2. For waist circumference, the reference group was <94 cm for men and <80 cm for women; increased and substantially increased 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/m^2.

Small cross-sectional studies of BMI in relation to AVS and/or aortic valve calcification have provided contradictory findings, with inverse,[14] neutral,[1] and positive[17–19] associations reported. Obesity has also been reported not to affect AVS progression,[24] and to improve outcome in AVS patients.[25,26] 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.[27] Our results for BMI confirm and extend the results from previous smaller prospective studies on AVS risk.[5,6] 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).[5] The 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/m^2 increase in BMI (corresponding to an HR of 1.22 per 5 kg/m^2) and 1.02 (95% CI 1.01–1.04) per 1 cm increase in WC.[6]

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.[12] Prospective studies have reported positive associations of hypertension[1,5,6] and levels of low-

density lipoprotein cholesterol[1,7] and lipoprotein(a)[1,10,11] with AVS risk. Moreover, genetically predicted higher levels of low-density lipoprotein cholesterol[7,9] and lipoprotein(a)[8,9,11] have been observed to be positively associated with AVS. Obesity, particularly excess visceral adiposity, is associated with an inflammatory state,[12,13] 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,[28] 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,[22] 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.

Funding

This work was supported by the Swedish Research Council/Medicine (2016-01042) and the Swedish Research Council/Research Infrastructures (2015-05997). The funders had no role in the design, collection, analysis, or interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication. The Open Access funding agency was the Swedish Research Council/Medicine (2016-01042).

Conflict of interest: none declared.

References

1. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997;**29**:630–634.
2. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. The Tromso study. *Heart* 2013;**99**:396–400.
3. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003;**24**:1231–1243.
4. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;**33**:2451–2496.
5. Martinsson A, Ostling G, Persson M, Sundquist K, Andersson C, Melander O, Engstrom G, Hedblad B, Smith JG. Carotid plaque, intima-media thickness, and incident aortic stenosis: a prospective cohort study. *Arterioscler Thromb Vasc Biol* 2014;**34**:2343–2348.
6. Eveborn GW, Schirmer H, Lunde P, Heggelund G, Hansen JB, Rasmussen K. Assessment of risk factors for developing incident aortic stenosis: the Tromso Study. *Eur J Epidemiol* 2014;**29**:567–575.
7. Smith JG, Luk K, Schulz CA, Engert JC, Do R, Hindy G, Rukh G, Dufresne L, Almgren P, Owens DS, Harris TB, Peloso GM, Kerr KF, Wong Q, Smith AV, Budoff MJ, Rotter JI, Cupples LA, Rich S, Kathiresan S, Orho-Melander M, Gudnason V, O'donnell CJ, Post WS, Thanassoulis G. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. *JAMA* 2014;**312**:1764–1771.
8. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, Kerr KF, Pechlivanis S, Budoff MJ, Harris TB, Malhotra R, O'brien KD, Kamstrup PR, Nordestgaard BG, Tybjaerg-Hansen A, Allison MA, Aspelund T, Criqui MH, Heckbert SR, Hwang SJ, Liu Y, Sjogren M, van der Pals J, Kalsch H, Muhleisen TW, Nothen MM, Cupples LA, Caslake M, Di Angelantonio E, Danesh J, Rotter JI, Sigurdsson S, Wong Q, Erbel R, Kathiresan S, Melander O, Gudnason V, O'donnell CJ, Post WS. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med* 2013;**368**:503–512.
9. Langsted A, Nordestgaard BG, Benn M, Tybjaerg-Hansen A, Kamstrup PR. PCSK9 R46L loss-of-function mutation reduces lipoprotein(a), LDL cholesterol, and risk of aortic valve stenosis. *J Clin Endocrinol Metab* 2016;**101**:3281–3287.
10. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol* 2014;**63**:470–477.
11. Arsenault BJ, Boekholdt SM, Dube MP, Rheaume E, Wareham NJ, Khaw KT, Sandhu MS, Tardif JC. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort. *Circ Cardiovasc Genet* 2014;**7**:304–310.
12. Gomez-Hernandez A, Beneit N, Diaz-Castroverde S, Escribano O. Differential role of adipose tissues in obesity and related metabolic and vascular complications. *Int J Endocrinol* 2016;**2016**:1216783.
13. Mathieu P, Lemieux I, Despres JP. Obesity, inflammation, and cardiovascular risk. *Clin Pharmacol Ther* 2010;**87**:407–416.
14. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkila J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. *Eur Heart J* 1994;**15**:865–870.
15. Dumesnil JG, Pibarot P. The obesity paradox in aortic stenosis: to be or not to be. *J Am Coll Cardiol* 2013;**62**:1691–1693.
16. Aksoy Y, Yagmur C, Tekin GO, Yagmur J, Topal E, Kekilli E, Turhan H, Kosar F, Yetkin E. Aortic valve calcification: association with bone mineral density and cardiovascular risk factors. *Coron Artery Dis* 2005;**16**:379–383.

17. Peltier M, Trojette F, Sarano ME, Grigioni F, Slama MA, Tribouilloy CM. Relation between cardiovascular risk factors and nonrheumatic severe calcific aortic stenosis among patients with a three-cuspid aortic valve. *Am J Cardiol* 2003;**91**:97–99.
18. Agmon Y, Khandheria BK, Meissner I, Sicks JR, O'fallon WM, Wiebers DO, Whisnant JP, Seward JB, Tajik AJ. Aortic valve sclerosis and aortic atherosclerosis: different manifestations of the same disease? Insights from a population-based study. *J Am Coll Cardiol* 2001;**38**:827–834.
19. Messika-Zeitoun D, Bielak LF, Peyser PA, Sheedy PF, Turner ST, Nkomo VT, Breen JF, Maalouf J, Scott C, Tajik AJ, Enriquez-Sarano M. Aortic valve calcification: determinants and progression in the population. *Arterioscler Thromb Vasc Biol* 2007;**27**:642–648.
20. Kuskowska-Wolk A, Karlsson P, Stolt M, Rossner S. The predictive validity of body mass index based on self-reported weight and height. *Int J Obes* 1989;**13**:441–453.
21. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;**894**:i–xii, 1–253.
22. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.
23. Fine J, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509.
24. Briand M, Lemieux I, Dumesnil JG, Mathieu P, Cartier A, Despres JP, Arsenault M, Couet J, Pibarot P. Metabolic syndrome negatively influences disease progression and prognosis in aortic stenosis. *J Am Coll Cardiol* 2006;**47**:2229–2236.
25. Rossi A, Gaibazzi N, Bellelli G, Nistri S, Cicoira M, Cioffi G, Faden G, Temporelli PL, Faggiano P. Obesity paradox in patients with aortic valve stenosis. Protective effect of body mass index independently of age, disease severity, treatment modality and non-cardiac comorbidities. *Int J Cardiol* 2014;**176**:1441–1443.
26. Rogge BP, Cramariuc D, Lonnebakken MT, Gohlke-Barwolf C, Chambers JB, Boman K, Gerdts E. Effect of overweight and obesity on cardiovascular events in asymptomatic aortic stenosis: a SEAS substudy (Simvastatin Ezetimibe in Aortic Stenosis). *J Am Coll Cardiol* 2013;**62**:1683–1690.
27. Thanassoulis G, Massaro JM, Cury R, Manders E, Benjamin EJ, Vasan RS, Cupple LA, Hoffmann U, O'donnell CJ, Kathiresan S. Associations of long-term and early adult atherosclerosis risk factors with aortic and mitral valve calcium. *J Am Coll Cardiol* 2010;**55**:2491–2498.
28. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Almeras N, Bergeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A, Despres JP. Hypertriglyceridemic waist: a marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? *Circulation* 2000;**102**:179–184.