

Traditional Cardiovascular Risk Factors and Their Relation to Future Surgery for Valvular Heart Disease or Ascending Aortic Disease: A Case–Referent Study

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Background—Risk factors for developing heart valve and ascending aortic disease are based mainly on retrospective data. To elucidate these factors in a prospective manner, we have performed a nested case–referent study using data from large, population-based surveys.

Methods and Results—A total of 777 patients operated for heart valve disease or disease of the ascending aorta had previously participated in population-based health surveys in Northern Sweden. Median time (interquartile range) from survey to surgery was 10.5 (9.0) years. Primary indications for surgery were aortic stenosis (41%), aortic regurgitation (12%), mitral regurgitation (23%), and dilatation/dissection of the ascending aorta (17%). For each case, referents were allocated, matched for age, sex, and geographical area. In multivariable models, surgery for aortic stenosis was predicted by hypertension, high cholesterol levels, diabetes mellitus, and active smoking. Surgery for aortic regurgitation was associated with a low cholesterol level, whereas a high cholesterol level predicted surgery for mitral regurgitation. Hypertension, blood pressure, and previous smoking predicted surgery for disease of the ascending aorta whereas diabetes mellitus was associated with reduced risk. After exclusion of cases with coronary atherosclerosis, only the inverse associations between cholesterol and aortic regurgitation and between diabetes mellitus and disease of the ascending aorta remained.

Conclusions—This is the first truly prospective study of traditional cardiovascular risk factors and their association with valvular heart disease and disease of the ascending aorta. We confirm the strong association between traditional risk factors and aortic stenosis, but only in patients with concomitant coronary artery disease. In isolated valvular heart disease, the impact of traditional risk factors is varying. (*J Am Heart Assoc.* 2017;6:e005133. DOI: 10.1161/JAHA.116.005133.)

Key Words: aortic disease • aortic regurgitation • aortic stenosis • mitral regurgitation

Diseases of heart valves and the ascending aorta, together with their surgical interventions, are associated with considerable morbidity and mortality, not least among older adults.^{1–5} Prevalences of these diseases are relatively high and increase with age.⁶ Several studies have addressed associated diseases and patterns of risk factors, but

importantly, most of these studies have been cross-sectional or retrospective in their design.^{7,8} Aortic stenosis has been extensively studied, and many traditional cardiovascular risk factors have been linked to this disease (eg, arterial hypertension, hypercholesterolemia, diabetes mellitus, and smoking).⁷ There are also negative interventional trials targeting traditional risk factors^{9–11} whereas prospective, observational studies of traditional cardiovascular risk factors and the risk for valvular disease and disease of the ascending aorta are lacking. Such investigations are cumbersome, so the nested case–referent design, which allows for truly prospective usage of baseline data, is an attractive and cost-effective strategy. In this study, we identified the surgical interventions for valvular heart disease and or disease of the ascending aorta performed within 3 large, population-based cohorts of Northern Sweden. We hypothesized that traditional cardiovascular risk factors are associated not only with coronary artery disease, but also with future development of valvular heart disease and or disease of the ascending aorta.

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Material and Methods

Study Population

Between March 1, 1988 and December 31, 2014, a total of 6681 patients underwent surgery for valvular heart disease and/or disease of the ascending aorta at the Department of Thoracic Surgery, Umeå University Hospital, Umeå, Sweden (the only cardiothoracic center in the northern healthcare region) with a catchment population of 878 152 (mean population 2005–2014). The region consists of 4 counties, and $\approx 2\%$ of the population are moving between these counties or to other counties each year.

Before their first surgery, 799 had participated in 1 of 3 population-based health studies in Northern Sweden: the Västerbotten Intervention Program (VIP); the Northern Sweden MONItoring Of trends and Determinants in CArdiovascular Disease (MONICA) survey; and the Mammary Screening Program (MSP). The contribution of cases from each survey was 619 (VIP), 101 (MONICA), and 79 (MSP).

VIP is an ongoing community intervention program that started in 1985, targeting cardiovascular disease and diabetes mellitus prevention.¹² Subjects are asked to participate in a health survey at their primary health center at the ages of 30, 40, 50, and 60 years. However, those aged 30 are no longer invited because of a lack of resources. The participation rate was initially 55%, but has increased and is now $\approx 65\%$. The total number of unique individuals surveyed in VIP was 99 268 as of December 31, 2014.

MONICA consists of randomly selected individuals aged 25 to 74 years from the counties of Västerbotten and Norrbotten who were invited to participate in a health study. The study started in 1986 and has been repeated 7 times with around 5-year intervals with new random samples of 2500 individuals each (the first 2 surveys invited 2000 individuals each).¹³ The overall participation rate was 74%, and a total of 12 368 unique persons participated through December 31, 2014.

Data for the MSP cohort, consisting of 28 778 women, were collected between 1995 and 2006 when the women attended their regular mammography exam and were asked to donate blood samples for research. In addition, anthropometric measurements were taken.

Four referents per case were randomly selected and matched for sex, age (± 2 years), type (MONICA, VIP, or MSP), and date (± 4 months) of health survey and geographical area. Referents and cases with a previous history of myocardial infarction, stroke, or cancer before survey were not excluded.

The study protocol was approved by the Regional Ethical Review Board in Umeå and complies with the Declaration of Helsinki. All participants gave written informed consent for future use of the data and blood samples.

Clinical Examinations at Baseline (Health Survey)

In VIP and MONICA, participants were asked to complete a health questionnaire about their living conditions and cardiovascular risk factors, and anthropometry and blood pressure (BP) were measured. An oral glucose tolerance test with measurements of fasting and postload glucose levels was routinely performed in VIP and in 60% of the MONICA participants, but was not obtained in MSP. Altogether, 75% of all subjects had a 2-hour 75-g oral glucose tolerance test at the time of the health survey. According to World Health Organization guidelines,¹⁴ the presence of diabetes mellitus was based on self-reported usage of antidiabetic medication and/or fasting plasma glucose levels ≥ 7.0 mmol/L and/or postload plasma glucose levels ≥ 11.1 mmol/L (≥ 12.2 mmol/L in the VIP, based on capillary plasma). Impaired fasting glucose was defined as a fasting glucose level ≥ 6.1 and < 7.0 mmol/L, and impaired glucose tolerance as a postload glucose level ≥ 7.8 and < 11.1 (≥ 8.9 and < 12.2 in VIP) in combination with a nondiabetic fasting glucose level.

In the MONICA and MSP surveys, BP was recorded in the sitting position after 5 minutes of rest, initially using a mercury sphygmomanometer, but since 2004 by using semiautomatic devices (Omron M7; Omron Corp, Kyoto, Japan). In the VIP survey, BP was measured after 5 minutes of rest in the recumbent position until September 1, 2009 and thereafter in the sitting position using devices as above. Measurements obtained in the recumbent position were adjusted according to a sex- and age-specific formula.¹⁵ Hypertension was defined as systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg and/or on antihypertensive medication.

Weight was measured without shoes in light indoor clothing and recorded to the nearest 0.2 kg. Height was measured to the nearest centimeter, without shoes, and body mass index (BMI) was calculated.

Subjects were categorized as daily smokers, ex-smokers, or nonsmokers. Total serum cholesterol was measured using a bench-top analyzer (Reflotron[®] Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany) at the time of the health survey (VIP, until September 1, 2009) or by an enzymatic method (Boehringer Mannheim GmbH Diagnostica) at a central laboratory (MONICA and VIP after September 1, 2009). Cholesterol values obtained using the bench-top method were adjusted to the results measured at the central laboratory.

In all studies, participants were asked to donate blood to be stored at -80°C for future research. Participants were fasting before sampling for a minimum of 4 hours (extended to 8 hours in 1992).

Clinical Examinations at Study End Point (Surgery)

Data from the preoperative assessments were extracted from hospital files and included medical history and cardiovascular risk factors, current medication, anthropometry, BP, and ECG and, if available, exercise stress test, coronary angiogram, chest x-ray, echocardiography, and results from blood chemistry. Perioperative details were recorded, such as the nature of valvular disease (eg, malformations, calcification, and endocarditis), type of valvular intervention (ie, mechanical or biological prosthesis, valvuloplasty), numbers of coronary grafts, cross-clamp, and bypass times, days of postoperative intensive care, and outcome (death during hospitalization or discharged).

The diagnosis of arterial hypertension, including BP measurements, diabetes mellitus, and smoking, at the preoperative assessment was obtained from the hospital files. BMI (kg/m^2) at surgery was calculated from weight and height routinely measured before the coronary angiography. The coronary angiogram, performed in 94% of all cases and according to established practice, was used to categorize coronary artery disease as follows: left main stem and 1-, 2-, or 3-vessel disease based on the presence of 1 or more stenoses with a diameter of at least 50%. The presence of stenosis less than 50% was considered to indicate coronary atherosclerosis. A preoperative echocardiographic investigation was performed in 96% of all cases. Left ventricular dimensions and stroke volume were retrieved from written reports, and ejection fraction was calculated according to the Teichholz formula.¹⁶ Most of the cases with missing preoperative angiographic and/or echocardiographic data had emergency surgery for disease of the ascending aorta. ECG was obtained in 97% of all cases, and heart rate and the presence of atrial fibrillation/flutter were recorded.

Statistical Analysis

Missing values for categorical variables were treated as a separate category not included in the presented tables, whereas missing continuous values in the logistic regression analysis were replaced by the median value representing the referents, ensuring a conservative result. Means and 95% CIs are presented, and differences in means between cases and referents were tested using Student's *t* tests. Continuous variables were categorized into quartiles by the distribution of the referent values, separately for men and women. Distribution of cases and referents was tested with a chi-squared test for linear association. Because cases and referents had the same follow-up time within strata in this nested and matched case–referent study, logistic regression analysis (rather than Cox regression) using the conditional maximum likelihood routine designed for matched analysis was used to estimate

odds ratios (ORs) and 95% CIs, and the influence of studied variables on valvular surgery (stratified for main indication and sex) was tested in univariate and multivariable models. In the multivariable analyses, a model including hypertension, total cholesterol, BMI, glucose tolerance and smoking was used. Glucose tolerance was tested both as separate categories (normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus) and as normal glucose tolerance versus impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus combined, when appropriate. In 2 subsequent models, hypertension was replaced by systolic and diastolic BP or glucose tolerance by fasting and postload glucose levels. The models were also tested after exclusion of cases with coronary artery disease, and after exclusion of cases with surgery within 5 years from the baseline survey to avoid studying phenomena secondary to established valvular heart disease, and, finally, the MSP cohort was excluded to test the impact of missing variables. All calculations were made using the statistical program, SPSS (version 23; IBM Corp, Armonk, NY).

Results

Characteristics at Study End Point (Surgery)

A total of 38% of patients were women, and median age (interquartile range) at surgery was 65.9 (13.9) years. Median time from health survey to surgery was 10.5 (9.1) years (aortic stenosis, 10.9 [CI 10.3–11.6]; aortic regurgitation, 9.0 [CI 7.7–10.2]; mitral regurgitation, 10.5 [CI 9.8–11.3]; ascending aorta, 10.0 [CI 9.0–11.0]). The only difference in time was between aortic stenosis and aortic regurgitation ($P=0.03$). General characteristics at surgery are given in Table 1. Among the initial 799 identified patients, 777 were included in this study, and their primary indications for surgery were aortic stenosis (41%), aortic regurgitation (12%), mitral regurgitation (23%), disease of the ascending aorta (17%), and coronary artery bypass (7%). The remaining 22 patients had other valvular interventions or were unclassifiable. All patients with coronary artery bypass as the primary indication had concomitant surgery for valvular disease and/or disease of the ascending aorta. Concomitant cardiac surgery, including coronary artery bypass, was performed in 34% to 46% of patients with primary valvular procedures. The corresponding proportion for primary ascending aorta disease was 62%. Three percent of the cases had previous coronary artery bypass whereas none had previous valvular or aortic intervention per protocol.

The surgical procedures for the interventions in aortic stenosis were biological prosthesis (54%), mechanical prosthesis (45%), and valvuloplasty (3%). The corresponding values for aortic regurgitation were 26%, 69%, and 5%; for mitral regurgitation, they were 11%, 22%, and 67%. Of those with

Table 1. Characteristics at Surgery

	AS	AR	MR	Ascending Aorta	CABG
n	322	91	181	131	52
Female sex, %	46.6 (41.1–52.1)	17.6 (9.6–25.6)	35.9 (28.9–43)	36.6 (28.3–45)	25.0 (12.8–37.2)
Age at surgery, y	67.5 (66.5–68.5)	59.7 (57.4–61.9)	64.1 (62.8–65.4)	60.7 (59.0–62.5)	68.7 (66.8–70.8)
Diabetes mellitus, %	15.8 (11.8–19.8)	1.1 (0.0–3.3)	7.2 (3.4–11.0)	4.6 (1.0–8.2)	13.5 (3.9–23.1)
Hypertension, %	56.8 (51.4–62.3)	36.3 (26.2–46.3)	39.4 (32.2–46.7)	54.2 (45.6–62.8)	69.2 (56.3–82.2)
BMI, kg/m ²	26.6 (26.1–27.1)	26.4 (25.7–27.1)	25.0 (24.5–25.5)	26.5 (25.8–27.2)	27.1 (25.8–28.5)
Smoking, %					
Never smoker	44.7 (39.3–50.2)	47.3 (36.8–57.7)	54.7 (47.4–62)	42.8 (34.2–51.3)	36.5 (23.0–50.1)
Current smoker	11.8 (8.3–15.3)	8.8 (2.9–14.7)	8.8 (4.7–13.0)	13.0 (7.2–18.8)	13.5 (3.9–23.1)
Ex-smoker	39.8 (34.4–45.1)	39.6 (29.3–49.8)	32 (25.2–38.9)	36.6 (28.3–45.0)	44.2 (30.3–58.2)
Coronary artery stenosis ≥50%, %	45.3 (39.9–50.8)	30.5 (20.3–40.7)	33.2 (26.2–40.1)	27.6 (18.6–36.6)	100
Stroke volume, mL	75.6 (73.5–77.9)	129.4 (121.1–137.7)	61.5 (58.7–64.4)	98.3 (91.7–104.9)	77.1 (71.6–83.1)
LVEDD, mm	49.5 (48.8–50.2)	66.2 (64.5–67.9)	60.2 (59.1–61.4)	53.7 (52.2–55.2)	52.7 (50.5–54.9)
LVESD, mm	31.0 (30.1–32)	47.0 (45.1–48.9)	39.5 (38.1–40.8)	35.2 (33.2–37.2)	35.6 (32.1–39.1)
Ejection fraction, %	61.5 (59.8–63.1)	51.7 (49.2–54.2)	57.0 (54.8–59.1)	58.2 (55.4–60.9)	57.1 (51.8–62.4)
Ejection fraction <50%, %	17.5 (12.7–22.3)	36.2 (25.5–47.0)	24.2 (17.4–31.0)	19.0 (10.1–27.8)	33.3 (17.2–49.5)
Heart rate, bpm	73 (71–75)	72 (69–75)	77 (74–80)	71 (68–74)	65 (61–68)
Atrial fibrillation or flutter, %	7.7 (4.7–10.7)	12.6 (5.5–19.8)	29.3 (22.5–36.1)	10.7 (5.1–16.2)	5.8 (0.0–12.3)
Concomitant surgery, %	46.3 (40.8–51.7)	44.0 (33.6–54.4)	34.3 (27.3–41.2)	61.8 (53.4–70.3)	100
AS	0.6 (0.0–1.6)	16.0 (9.7–22.4)	63.5 (49.9–77.0)
AR	0.3 (0.0–0.9)	...	2.2 (0–4.4)	37.4 (29.0–45.8)	9.6 (1.3–17.9)
MR	0.3 (0.0–0.9)	6.6 (1.4–11.8)	...	0.8 (0.0–2.3)	21.2 (9.7–32.6)
Ascending aorta	14.9 (11.0–18.8)	23.1 (14.3–31.9)	1.1 (0.0–2.6)	...	7.7 (0.2–15.2)
CABG	33.9 (28.7–39.0)	14.3 (7.0–21.6)	28.7 (22.1–35.4)	13.0 (7.1–18.8)	...
Other	1.2 (0.0–2.5)	3.3 (0.0–7.0)	6.1 (2.6–9.6)	5.3 (1.4–9.2)	5.8 (0.0–12.3)
Concomitant medication, %					
Beta-blockers	44.4 (39.0–49.9)	39.6 (29.3–49.8)	43.1 (35.8–50.4)	35.4 (27.1–43.7)	69.2 (56.3–82.2)
ACEi/ARB	29.5 (24.4–34.5)	53.9 (43.4–64.3)	65.8 (58.8–72.7)	37.7 (29.3–46.1)	46.2 (32.1–60.2)
Spironolactone	4.4 (2.1–6.6)	5.5 (0.7–10.3)	8.3 (4.2–12.3)	2.3 (0.0–4.9)	1.9 (0.0–5.8)
Diuretics	35.4 (30.1–40.7)	26.4 (17.1–35.6)	42.5 (35.3–49.8)	21.5 (14.4–28.7)	28.8 (16.1–41.6)
Digoxin	3.1 (1.2–5.1)	7.7 (2.1–13.3)	14.9 (9.7–20.2)	2.3 (0.0–4.9)	1.9 (0.0–5.8)
Calcium-channel blockers	21.3 (16.8–25.8)	11.0 (4.4–17.5)	9.4 (5.1–13.7)	20.0 (13.0–27.0)	32.7 (19.5–45.9)
Aspirin	41.7 (36.3–47.1)	28.6 (19.1–38)	24.9 (18.5–31.2)	20.8 (13.7–27.8)	73.1 (60.6–85.5)
Warfarin	8.5 (5.4–11.5)	14.3 (7–21.6)	24.3 (18.0–30.6)	11.5 (6.0–17.1)	7.7 (0.2–15.2)
Statins	39.2 (33.8–44.6)	19.8 (11.4–28.1)	23.8 (17.5–30)	19.2 (12.4–26.1)	53.8 (39.8–67.9)
Clopidogrel	5.3 (2.9–7.8)	5.5 (0.7–10.3)	3.3 (0.7–5.9)	1.5 (0.0–3.7)	13.5 (3.9–23.1)

Values shown are numbers, means, proportions, and 95% CIs at surgery, stratified for primary surgical intervention. ACE-I indicates angiotensin-converting enzyme inhibitor; AR, aortic regurgitation; ARB, angiotensin receptor blocker; AS, aortic stenosis; ascending aorta, disease of the ascending aorta; BMI, body mass index; CABG, coronary artery bypass graft; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation.

surgery for ascending aortic disease, 34% had an acute dissection. The etiology for mitral regurgitation was available in 97% of the cases and was dilatation of annulus 24%, rupture of chordae 48%, mitral valve prolapse 20%, and other 5%.

Concomitant coronary artery disease was present in 59% of patients with aortic stenosis, 47% of patients with mitral regurgitation, 42% with ascending aortic disease, and 39% with aortic regurgitation. Impaired left ventricular systolic

function, defined as an ejection fraction less than 50%, was observed in 17.5% to 36.2% of the patients with the highest prevalence among patients with aortic regurgitation. Heart rate measured from the preoperative ECG recording showed a lower heart rate for those with a primary indication for coronary artery disease. Almost one-third of the patients with mitral regurgitation had atrial fibrillation or atrial flutter whereas the occurrence ranged between 6% and 13% in the other groups. The majority of patients were prescribed cardiovascular-acting drugs, especially in those with primary surgery because of coronary artery disease.

Characteristics at Baseline (Health Survey)

At the baseline survey, patients with a future surgical intervention for a significant aortic stenosis had higher levels of BMI, fasting glucose, cholesterol, and systolic and diastolic BP compared with referents. Prevalences of diabetes mellitus, hypertension, and smoking were higher (Table 2). In contrast, patients with future surgery for aortic regurgitation had lower cholesterol levels. Diabetes mellitus was also less frequent in this group, which had a lower level of education before surgery. Similarly, patients with a mitral regurgitation had lower cholesterol levels than referents before surgery. Of note, subjects with future disease of the ascending aorta had less diabetes mellitus whereas arterial hypertension and higher levels of diastolic BP were more common. Furthermore, they were more often active smokers.

Predictors of Future Surgery

In the univariate analysis, surgery for aortic stenosis was predicted by arterial hypertension, high systolic and diastolic BPs, high levels of cholesterol, diabetes mellitus, overweight, and active smoking (Table 3). High systolic and diastolic BP, high cholesterol, and high BMI associated with surgery irrespective if tested as categorized or as continuous variables, and tests for trend were statistically significant. Hypertension, high cholesterol levels, diabetes mellitus, and active smoking remained associated with future surgery in a multivariable model (Table 3). Further modeling replacing diabetes mellitus with glucose levels or replacing arterial hypertension with systolic and diastolic BP provided similar outcomes (data not shown). Fasting and postload glucose levels did not predict aortic stenosis in any model (data not shown). Arterial hypertension (OR, 1.93 [1.38–2.70]), high cholesterol levels (OR, 1.62 [1.02–2.55]), and active smoking (OR, 1.73 [1.19–2.50]) remained associated with surgery for aortic stenosis after exclusion of patients with surgery within 5 years from the baseline survey. After stratification for sex, the point estimates were similar in men and women,

and arterial hypertension remained associated with aortic stenosis in both sexes (OR, 1.75 for men [1.19–2.58]; OR, 2.14 for women [1.26–3.64]). After exclusion of patients with coronary artery disease in the preoperative angiogram, none of the risk factors remained associated with surgery for aortic stenosis, although the point estimate for arterial hypertension remained elevated (OR, 1.52 [0.93–2.48]). Similar results were obtained after exclusion of the MSP cohort (data not shown).

Aortic regurgitation was not predicted by any of the traditional risk factors. Of note, a high cholesterol level was associated with reduced risk for future valvular surgery, and this effect persisted in the multivariable model (Table 3) and after exclusion of patients with coronary artery disease (OR, 0.21 [0.06–0.81]) or after exclusion of the MSP cohort (OR, 0.29 [0.12–0.71]). The point estimate remained low, although not significant (OR, 0.41 [0.15–1.11]), after exclusion of patients with surgery within 5 years from the baseline survey. A diastolic BP above the median was associated with reduced risk for surgery for aortic regurgitation, as was also the case in the multivariable model in which arterial hypertension was replaced with systolic and diastolic BPs (Q₃_{DBP}, 0.27 [0.11–0.64]; Q₄_{DBP}, 0.35 [0.13–0.92]). These associations did not remain after exclusion of patients with surgery within 5 years of the baseline survey.

A high cholesterol level predicted surgery for mitral regurgitation whereas none of the other traditional cardiovascular risk factors were associated with mitral valve surgery (Table 3). The stratified analysis for sex did not provide more information. Cholesterol levels were not associated with surgery for mitral regurgitation in patients without coronary artery disease or in those with surgery more than 5 years from the baseline survey. Similar results were observed after exclusion of the MSP cohort (data not shown).

Arterial hypertension, systolic and diastolic BP, and previous smoking predicted surgery for disease of the ascending aorta whereas diabetes mellitus was associated with reduced risk in both the uni- and multivariable models (Table 3). In the multivariable model replacing hypertension with measured levels of BP, diastolic—but not systolic—BP predicted surgery without additive information in the stratified analysis for sex (data not shown). Arterial hypertension (OR, 2.36 [1.34–4.17]) and previous smoking (OR, 2.15 [1.16–3.99]) remained associated with surgery for disease of the ascending aorta after exclusion of patients with surgery within 5 years from the baseline survey. Only glucose intolerance remained protective when patients with coronary disease were excluded from the model (OR, 0.24 [0.07–0.81]). The point estimates remained elevated for hypertension and previous smoking, although not significantly. After exclusion of the MSP cohort, similar results were observed (data not shown).

Table 2. Characteristics at Survey

	AS			AR			MR			Ascending Aorta		
	Cases	Referents	P Value	Cases	Referents	P Value	Cases	Referents	P Value	Cases	Referents	P Value
n	322	1276		91	358		181	717		131	521	
Female sex, %	46.6 (41.1–52.1)	46.7 (44–49.4)	0.97	17.6 (9.6–25.6)	17.3 (13.4–21.3)	0.95	35.9 (28.9–43.0)	35.4 (31.9–38.9)	0.90	36.6 (28.3–45.0)	36.3 (32.1–40.4)	0.94
Age at survey, y	56.6 (55.7–57.6)	56.6 (56.1–57)	0.91	49.7 (47.6–51.9)	50.9 (49.9–51.9)	0.86	53.6 (52.3–54.8)	53.6 (52.9–54.2)	0.99	51.5 (49.9–53.2)	51.5 (50.7–52.3)	0.96
BMI, kg/m ²	26.8 (26.3–27.3)	26.1 (25.9–26.3)	0.004	26.4 (25.7–27.1)	26.6 (26.2–27)	1.00	25.4 (24.7–26.0)	25.9 (25.6–26.2)	0.09	26.0 (25.3–26.7)	26.2 (25.9–26.5)	0.64
Fasting glucose, mmol/L	5.6 (5.4–5.8)	5.4 (5.3–5.4)	0.02	5.2 (5.1–5.4)	5.4 (5.3–5.5)	0.24	5.3 (5.2–5.4)	5.5 (5.4–5.6)	0.04	5.3 (5.2–5.4)	5.4 (5.3–5.5)	0.13
Postload glucose, mmol/L	6.7 (6.4–6.9)	6.6 (6.5–6.7)	0.45	6.2 (5.8–6.5)	6.4 (6.1–6.6)	0.47	6.7 (6.4–7.1)	6.6 (6.4–6.7)	0.37	6.4 (6–6.7)	6.6 (6.4–6.8)	0.22
Diabetes mellitus, %	9.8 (6.0–13.7)	5.7 (4.2–7.3)	0.05		4.7 (2.4–7)		4.2 (0.9–7.6)	7.0 (4.9–9.1)	0.17	0.9 (0.0–2.7)	6.2 (3.9–8.5)	<0.001
Total cholesterol, mmol/L	6.4 (6.3–6.6)	6.2 (6.2–6.3)	0.02	5.6 (5.4–5.8)	6.0 (5.9–6.1)	0.01	6.3 (6.1–6.4)	5.9 (5.9–6.0)	0.03	5.9 (5.7–6.1)	6.0 (5.9–6.1)	0.27
Smoking, %			0.10						0.31			0.03
Never smoker	30.1 (25.1–35.2)	36.1 (33.5–38.8)		38.5 (28.3–48.7)	41.6 (36.5–46.8)		42.0 (34.7–49.2)	37.5 (34–41.1)		31.3 (23.3–39.3)	40.1 (35.9–44.3)	
Current smoker	17.7 (13.5–21.9)	18.5 (16.4–20.6)		19.8 (11.4–28.1)	20.7 (16.5–24.9)		14.9 (9.7–20.2)	19.1 (16.2–22.0)		26.7 (19.0–34.4)	17.1 (13.8–20.3)	
Ex-smoker	30.7 (25.7–35.8)	26.2 (23.8–28.6)		31.9 (22.1–41.6)	29.3 (24.6–34.1)		28.2 (21.6–34.8)	30.4 (27.0–33.8)		29.8 (21.8–37.7)	30.9 (26.9–34.9)	
Hypertension, %	60.4 (54.5–66.3)	46.6 (43.6–49.6)	<0.001	45.2 (34.4–56.1)	41.2 (35.8–46.5)	0.50	39.9 (32.2–47.6)	43.5 (39.6–47.4)	0.40	51.3 (42–60.7)	37.2 (32.8–41.7)	0.01
SBP, mm Hg	139 (137–141)	135 (134–136)	0.001	135 (131–138)	132 (130–134)	0.18	132 (130–135)	133 (131–134)	0.90	133 (130–136)	131 (129–132)	0.14
DBP, mm Hg	85 (84–87)	84 (83–84)	0.001	81 (78–83)	84 (83–85)	0.08	83 (82–85)	84 (84–85)	0.37	86 (84–88)	82 (82–83)	<0.001
University education, %	13.8 (9.6–18.1)	16.2 (13.9–18.5)	0.35	8.3 (2.3–14.4)	19.6 (15.2–23.9)	0.03	16.7 (10.8–22.6)	18.9 (15.8–22.0)	0.52	15.8 (9.0–22.6)	20.0 (16.3–23.7)	0.28

Values shown are numbers, means, proportions, P values, and 95% CIs for cases and referents at survey, stratified for primary surgical intervention. AR indicates aortic regurgitation; AS, aortic stenosis; ascending aorta, disease of the ascending aorta; BMI, body mass index; DBP, diastolic blood pressure; MR, mitral regurgitation; SBP, systolic blood pressure.

Table 3. Predictors of Valvular Disease

Variable	AS				AR				MR				Ascending Aorta								
	Referents	Cases	Trend	Univariate	Multi-variable	Referents	Cases	Trend	Univariate	Multi-variable	Referents	Cases	Trend	Univariate	Multi-variable	Referents	Cases	Trend	Univariate	Multi-variable	
Hypertension																					
No	561	105	<0.0001	1.00	1.00	193	46	0.50	1.00	1.00	354	95	0.41	1.00	1.00	290	55	0.01	1.00	1.00	
Yes	490	160		1.90 (1.41–2.54)	1.87 (1.37–2.54)	135	38		1.24 (0.73–2.08)	1.20 (0.69–2.09)	273	63		0.84 (0.57–1.24)	0.88 (0.58–1.32)	172	58		2.07 (1.29–3.33)	2.42 (1.44–4.06)	
SBP																					
Q1	254	45	0.001	1.00		91	19	0.51	1.00		165	34	0.97	1.00		144	27	0.03	1.00		
Q2	270	54		1.18 (0.75–1.85)		89	27		1.49 (0.75–2.95)		161	50		1.53 (0.93–2.52)		128	25		1.11 (0.60–2.05)		
Q3	240	77		1.95 (1.28–2.97)		78	17		1.09 (0.51–2.33)		154	42		1.37 (0.80–2.36)		107	35		2.03 (1.09–3.79)		
Q4	287	90		2.01 (1.30–3.10)		70	21		1.56 (0.73–3.35)		147	32		1.07 (0.59–1.93)		83	26		2.06 (1.04–4.07)		
Continuous				1.02 (1.01–1.02)					1.01 (1.00–1.03)					1.00 (0.99–1.01)					1.01 (1.00–1.03)		
DBP																					
Q1	313	57	0.001	1.00		102	34	0.21	1.00		180	43	0.94	1.00		153	25	0.01	1.00		
Q2	231	55		1.38 (0.90–2.10)		74	18		0.70 (0.36–1.35)		145	30		0.85 (0.50–1.46)		104	24		1.49 (0.79–2.83)		
Q3	281	76		1.58 (1.06–2.36)		87	15		0.48 (0.24–0.98)		159	59		1.61 (1.00–2.58)		121	32		1.78 (0.97–3.27)		
Q4	226	77		2.03 (1.36–3.04)		65	17		0.77 (0.39–1.54)		143	26		0.77 (0.44–1.35)		84	32		2.67 (1.41–5.06)		
Continuous				1.02 (1.01–1.04)					0.97 (0.95–1.00)					0.99 (0.97–1.01)					1.05 (1.02–1.07)		

Continued

Table 3. Continued

Variable	AS				AR				MR				Ascending Aorta								
	Referents	Cases	Trend	Univariate	Multi-variable	Referents	Cases	Trend	Univariate	Multi-variable	Referents	Cases	Trend	Univariate	Multi-variable	Referents	Cases	Trend	Univariate	Multi-variable	
Glucose tolerance																					
NGT	720	173	0.06	1.00	1.00	250	68	0.07	1.00	1.00	459	113	0.40	1.00	1.00	334	89	0.05	1.00	1.00	
IFG	86	26		1.32 (0.81–2.16)	1.24 (0.75–2.06)	33	8		0.89 (0.39–2.05)	0.89 (0.37–2.11)	56	14		0.98 (0.52–1.85)	1.03 (0.54–1.99)	36	13		1.35 (0.69–2.65)	1.10 (0.52–2.35)	
IGT	63	12		0.80 (0.42–1.54)	0.73 (0.38–1.42)	21	5		0.86 (0.32–2.33)	0.86 (0.30–2.47)	30	9		1.17 (0.53–2.57)	1.13 (0.50–2.54)	36	7		0.71 (0.29–1.72)	0.71 (0.29–1.77)	
DM	53	23		1.89 (1.10–3.23)	1.78 (1.01–3.11)	15	0		–	–	41	6		0.56 (0.22–1.42)	0.62 (0.24–1.60)	27	1		0.13 (0.02–1.01)	0.09 (0.01–0.73)	
BMI																					
Q1	326	62	0.01	1.00	1.00	89	16	0.52	1.00	1.00	175	55	0.10	1.00	1.00	124	34	0.92	1.00	1.00	
Q2	304	77		1.33 (0.92–1.93)	1.26 (0.86–1.85)	71	23		1.83 (0.91–3.72)	1.99 (0.94–4.19)	196	50		0.81 (0.52–1.26)	0.77 (0.49–1.22)	138	30		0.78 (0.45–1.37)	0.75 (0.42–1.35)	
Q3	311	79		1.35 (0.93–1.95)	1.14 (0.78–1.67)	92	27		1.67 (0.85–3.32)	1.92 (0.92–3.99)	182	37		0.66 (0.42–1.04)	0.64 (0.40–1.04)	126	29		0.84 (0.48–1.46)	0.81 (0.45–1.46)	
Q4	317	98		1.65 (1.16–2.36)	1.34 (0.92–1.94)	102	25		1.39 (0.69–2.78)	1.55 (0.71–3.37)	159	36		0.71 (0.44–1.16)	0.70 (0.42–1.17)	127	35		1.01 (0.57–1.78)	0.82 (0.44–1.54)	
Continuous				1.05 (1.01–1.08)					1.00 (0.94–1.07)					0.96 (0.92–1.01)					0.99 (0.93–1.04)		
Cholesterol																					
Q1	262	51	0.02	1.00	1.00	93	30	0.04	1.00	1.00	163	35	0.24	1.00	1.00	125	34	0.26	1.00	1.00	
Q2	220	55		1.30 (0.85–1.98)	1.32 (0.85–2.04)	86	25		0.89 (0.49–1.63)	0.79 (0.42–1.49)	171	46		1.29 (0.78–2.15)	1.32 (0.78–2.22)	125	36		1.05 (0.60–1.81)	1.08 (0.60–1.97)	
Q3	278	67		1.27 (0.84–1.91)	1.21 (0.79–1.84)	88	22		0.78 (0.41–1.48)	0.64 (0.32–1.28)	149	28		0.90 (0.51–1.59)	0.94 (0.53–1.67)	116	22		0.68 (0.36–1.28)	0.65 (0.33–1.27)	
Q4	281	89		1.70 (1.14–2.56)	1.64 (1.07–2.49)	68	9		0.40 (0.18–0.93)	0.29 (0.12–0.71)	145	47		1.59 (0.93–2.69)	1.74 (1.01–3.00)	91	20		0.80 (0.41–1.56)	0.80 (0.39–1.62)	

Continued

Table 3. Continued

Variable	AS			AR			MR			Ascending Aorta					
	Referents	Cases	Trend	Univariate	Multi-variable	Referents	Cases	Trend	Univariate	Multi-variable	Referents	Cases	Trend	Univariate	Multi-variable
Continuous				1.16 (1.03–1.31)					0.72 (0.56–0.92)					1.22 (1.02–1.44)	
Smoking															
Never smoker	461	97	0.28	1.00	1.00	149	35	0.83	1.00	1.00	269	76	0.09	1.00	1.00
Current smoker	334	99		1.44 (1.04–1.99)	1.49 (1.06–2.08)	105	29		1.22 (0.69–2.15)	1.24 (0.68–2.23)	218	51		0.83 (0.55–1.24)	0.92 (0.61–1.40)
Ex-smoker	236	57		1.18 (0.81–1.71)	1.29 (0.88–1.90)	74	18		1.04 (0.55–1.98)	1.07 (0.55–2.09)	137	27		0.69 (0.42–1.13)	0.65 (0.39–1.09)

Values shown are numbers (referents, cases), *P* for trend, and odds ratios (95% CIs), stratified for primary surgical intervention. Cutoffs for quartiles (Q1–Q4) were stratified for sex (men and women): SBT 122.6, 131.1, 142.6 and 117.8, 130.8, 144.4, respectively; DBT 78.9, 83.6, 91.3 and 78.8, 81.7, 88.7, respectively; BMI 23.9, 25.9, 28.1 and 22.8, 25.1, 28.2, respectively; and cholesterol 5.3, 6.1, 6.8 and 5.5, 6.2, 6.8, respectively. AR indicates aortic regurgitation; AS, aortic stenosis; ascending aorta, disease of the ascending aorta; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MR, mitral regurgitation; NGT, normal glucose tolerance; SBP, systolic blood pressure.

Discussion

This is the first prospective, observational study of possible associations between traditional risk factors and valvular heart disease. We found that classical cardiovascular risk factors predicted surgery for aortic stenosis and disease of the ascending aorta, but no other valvular diseases. However, none of these factors remained predictive of valvular heart disease after exclusion of patients with coronary artery disease. Of note, cholesterol and diabetes mellitus were inversely associated with aortic regurgitation and diseases of the ascending aorta, respectively, and no major sex-related differences were found in these associations.

Aortic Stenosis

Surgery for aortic stenosis is the most common valvular intervention in the population and is associated with significant morbidity and mortality.¹⁷ There are no known methods to halt the process, and surgery is the ultimate treatment.¹⁸ Several studies have focused on an association between aortic stenosis and traditional cardiovascular risk factors. In a cross-sectional study of 5201 subjects older than 65 years, age, sex, lipoprotein(a), low-density lipoprotein cholesterol, smoking, and history of hypertension were more common in subjects with aortic sclerosis and aortic stenosis.⁷ Three randomized trials (SALTIRE [Stenosis and Lipid Lowering Trial, Impact on Regression], SEAS [Simvastatin and Ezetimibe in Aortic Stenosis], and ASTRONOMER [Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin]) have tested the hypothesis that statins slow the progression rate and reduce the risk for aortic valvular replacement.^{9–11} The process leading to aortic stenosis resembles vascular wall atherosclerosis, and animal and retrospective human studies have indicated that statin use can slow the progress of aortic stenosis. However, none of the 3 studies showed any effect on progression rate, and plausible explanations might be late initiation of treatment of an advanced valvular disease, the existence of several phenotypes of the disease, or the existence of as-yet unknown risk factors. Aortic stenosis also exhibit unexplained sex-related differences in occurrence, pathophysiology, and prognosis.^{19–21} Other pathways may be important; recently, high-sensitivity C-reactive protein was reported to be an independent risk marker for aortic valvular replacement in the SEAS study, suggesting that inflammatory processes may be important.²² We have previously shown a cross-sectional association between high levels of leptin, lipoprotein(a), and tissue plasminogen activator mass and aortic stenosis requiring surgery.²³

In this study, with a focus on traditional risk factors, we found that hypertension, high cholesterol levels, a diagnosis of diabetes mellitus, and active smoking predicted independently

the development of aortic stenosis, also after exclusion of patients with surgery within 5 years from the baseline survey. However, after exclusion of cases with visible coronary artery disease, none of the risk factors remained significant, although possibly indicating an effect of hypertension, which was also observed in the SEAS trial.²⁴ Of note, valvular defects, such as bicuspid valves, were not studied as predictors because echocardiography was not performed at baseline. Clearly, more research is needed to identify risk factors amenable for intervention.²⁵ Our study, with well-characterized phenotypes, shows the importance of separating isolated aortic valvular disease from concomitant coronary artery disease.

Aortic Regurgitation

Known risk factors for developing aortic regurgitation are bicuspid aortic valve, diseases of the ascending aorta, such as Marfan syndrome, endocarditis, and other valvular malformations.² To our knowledge, no other prospective studies have linked cardiovascular risk factors with the risk for developing significant aortic regurgitation. In our study, we unexpectedly found that only low levels of cholesterol predicted valvular replacement attributed to aortic regurgitation. However, hypocholesterolemia has previously been associated with vascular morbidity (eg, cerebral haemorrhage and total mortality).^{26,27} We found that low education predicted aortic regurgitation. Education is an established proxy for socioeconomic status that, in turn, is associated with risk of cardiovascular disease, including valvular disease.^{28,29} Thus, our data are in line with previous observations.

Mitral Regurgitation

Mitral regurgitation is commonly reported from clinical and echocardiographic examinations, and the clinical significance is not always evident.⁶ In this study, only mitral regurgitation requiring surgery was included. Mitral regurgitation has a diverse etiology ranging from left ventricular dilatation to primary structural valvular defects.^{2,5,30} Furthermore, the defects could be acquired or congenital, and the spectrum differs between developed and developing countries (eg, rheumatic fever). We found no association between classical cardiovascular risk factors and future surgery for mitral regurgitation after exclusion of coronary atherosclerosis. To our knowledge, no other studies have investigated whether cardiovascular risk factors predict mitral valvular surgery.

Ascending Aorta

In our analysis, the classical cardiovascular risk factors, excluding diabetes mellitus, predicted diseases of the ascending aorta. Of note, a diagnosis of diabetes mellitus

was related to reduced risk. In cross-sectional studies, diseases of the ascending aorta have been inversely related to diabetes mellitus and associated with less systemic atherosclerosis, and an inverse association between aortic root diameter and diabetes mellitus has been demonstrated.^{31,32} Furthermore, diabetes mellitus was less frequent among patients discharged for thoracic aortic aneurysms and dissections in a nation-wide US study compared with controls.³³ This might be attributed to increased extracellular matrix deposition in the aortic wall in patients with diabetes mellitus. Even with exclusion of those with coronary artery disease, the inverse association between disease of the ascending aorta and diabetes mellitus remained.

Strengths and Limitations

We suggest that these findings have a high degree of generalizability for the following reasons. The study relies on long-lasting, population-based surveys in a region with very high attendance rates. However, the inclusion criteria for the VIP survey should be emphasized because they are expected to have affected the age distribution of the patient population, that is, persons are included if they have had a health survey at 30, 40, 50, or 60 years. The mean age in our material was 64.9 years, and in the 5892 outside the study 67.8 years. The proportion of women was 38% versus 37%. Thus, our cohort was slightly, but significantly, younger because of the age limits of the surveys whereas there is no upper age limit for surgery in the general population.

Characteristics of nonparticipants have been analyzed in the MONICA survey, and the attendance rate of smoking younger persons with lower education has been declining,¹² so this group could be under-represented in our study. Data were missing in the MSP cohort per protocol; however, the statistical model remained stable when tested without the MSP cohort. This study is truly prospective because of the nested case-referent design, which minimizes the risk for selection and recall biases. Furthermore, all cases were identified at the thoracic surgery department at the University Hospital of Umeå, where almost all surgical interventions for valvular and ascending aorta disease are performed in the region, and a single-center study ensures uniform routines and indications for surgery. All cases in this study were deemed operable by the thoracic surgeon, which probably means that patients with multiple comorbidities and unacceptably high perioperative risk are under-represented. In contrast to the prospective baseline survey data, pre- and perioperative data were collected from hospital files and were thus retrospective in nature. However, all interventions were classified by an experienced cardiologist in the study team blinded for baseline survey data and outcomes. Furthermore, despite the size of the study, stratification was hampered by lack of power, and we cannot exclude

associations of lower strength than those found in this study. Finally, the date of onset of valvular disease and disease of the ascending aorta is not possible to determine and cases may already have had an ongoing and asymptomatic process in the valve or and in the ascending aorta that could have affected the measurements at baseline, for example, the association between diastolic BP at baseline and future surgery for aortic regurgitation. This was tested by excluding patients with surgery within 5 years from the baseline survey, which corresponded approximately to the lowest quartile of the time period from health survey to surgery. Furthermore, because of the nature of the study end point (ie, valvular or aortic surgery), the results can only be generalized to patients requiring intervention. However, valvular disease is usually a progressive disease that eventually needs surgical intervention.

We conclude that with a median time of almost 10 years and in those with concomitant coronary arteriosclerosis, traditional risk factors predicted future surgery for aortic stenosis and disease of the ascending aorta, whereas these risk factors did not predict surgery for aortic or mitral regurgitation. Of note, many of these factors did not predict surgery in those without coronary atherosclerosis. Risk factors for valvular diseases are thus yet to be identified, and we hope that further analysis of this cohort may yield truly modifiable risk factors. The unexpected associations between metabolic factors and aortic regurgitation and disease of the ascending aorta warrant further investigation.

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Disclosures

None.

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