Original Article

Familial Aggregation of Aortic Valvular Stenosis
A Nationwide Study of Sibling Risk

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Background—Aortic valvular stenosis (AS) is the most common cause of cardiac valvular replacement surgery. During the last century, the pathogenesis of AS has undergone transitions in developed countries, from rheumatic heart disease to a degenerative calcific pathogenesis. Although a familial component has been described for a subset of cases with a bicuspid valve, data are limited on the overall familial aggregation of this disease.

Methods and Results—Contemporary information on 6 117 263 Swedish siblings, of which 13 442 had a clinical diagnosis of AS, was collected from the nationwide Swedish Multi-Generation Register and the National Patient Register. A total of 4.8% of AS cases had a sibling history of AS. Having at least 1 sibling with AS was associated with a hazard ratio of 3.41 (95% confidence interval, 2.23–5.21) to be diagnosed with AS in an adjusted model. Individuals with >1 sibling with AS had an exceptionally high risk (hazard ratio, 32.84) but were uncommon (34 siblings from 11 sibships). In contrast, spouses of subjects with AS were only slightly more likely to be diagnosed with AS compared with subjects without spousal AS (hazard ratio 1.16 for husbands and 1.18 for wives).

Conclusions—A sibling history of clinically diagnosed AS was associated with increased risk of AS. Spouses of patients with AS only had a modest risk increase, suggesting that shared adult environmental factors contribute less to the development of AS than genetic factors. (*Circ Cardiovasc Genet.* 2017;10:e001742. DOI: 10.1161/CIRCGENETICS.117.001742.)

Key Words: aortic valve stenosis ■ risk ■ siblings ■ valvular heart diseases

Aortic valvular stenosis (AS) is a common valvular disease with a prevalence of 0.3% to 0.5% in the population and is the most common cause of valvular replacement therapy.[1] Age is one of the most important risk factors for AS, and the prevalence increases strikingly with age to estimates of 2% to 7% in the population for 65 years.[1–5] AS has several clinical presentations, from a murmur on cardiac auscultation in asymptomatic subjects to severely debilitating disease. The most common symptoms include dyspnea, angina pectoris, and syncope.[2] Symptomatic disease has a poor prognosis with a projected mortality rate of 30% to 50% in 5 years if left untreated.[2,3,6]

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In the 20th century, developed countries have seen a shift in the main pathogenesis for AS from rheumatic disease to a progressive degenerative process, including lipid accumulation and inflammation, similar to atherosclerosis.[7–10] AS today shares several clinical risk factors with atherosclerotic disease, such as diabetes mellitus, hypertension, and smoking.[11,12] There is currently no established medical therapy for manifest AS, with 3 large randomized trials showing no effect of lipid-lowering medications on the progression of the disease.[13–15] However, outcomes in AS have improved in recent decades, likely because of improved risk factor control at an earlier stage, improved treatment of common comorbidities, such as coronary heart disease, and increased use of aortic valve replacement in the elderly in combination with reduced perioperative mortality.[16]

In addition to environmental factors, genetic factors are important for the development of atherosclerotic disease.[17] Similarly, familial aggregation of cases undergoing aortic valve surgery has been reported in certain regions of western France, but no systematic investigation of family aggregation of AS in the general population has been reported.[18] A familial component has been shown for bicuspid aortic valve (BAV)—a congenital cardiac malformation, which is an important cause of AS in the young.[19–21] There is, however, a lack of large, population-based studies that have examined familial aggregation across the whole spectrum of AS.

The aim of this study was to investigate the familial aggregation of AS in Swedish nationwide population data using a sibling design.

Methods

Study Sample

All siblings in the Swedish population born after 1932 were included (0–78 years old) using nationwide registers. Inclusion criteria were individuals alive in 1997 with at least 1 sibling. Subjects with a hospital discharge diagnosis of AS as primary or secondary diagnosis were identified from the National Inpatient Register (NPR)[22] using *International Classification of Diseases* (*ICD*) codes described below. Follow-up extended until 2010. Reporting to the NPR has been nationwide and mandatory since 1987. Sweden has a tax-funded healthcare system with reimbursement linked to diagnosis codes.

The Multi-Generation Register[23] contains information on first-degree relatives, including information on parents and siblings of index individuals with close to universal inclusion. The NPR was linked to the Multi-Generation register using the unique Swedish personal identification number that all Swedish citizens with residence permit receive.[24] Anonymity was preserved by replacing the personal identification number with a unique serial number for each individual. The local ethics committee in Lund approved of the study.

Case Ascertainment

Primary diagnosis of the valvular heart diseases, including AS, has previously been shown to be highly valid (>90% positive predictive value) in the NPR.[22,25] Validation studies have also described that registered cases of AS are typically of moderate-to-severe grade and thus generally represent clinically relevant disease. The diagnoses have been shown to primarily be based on echocardiographic examination.[25]

The *ICD* of the World Health Organization is the basis for diagnosis coding in the NPR. The ninth version was used from 1987 until 1996 and the 10th version from 1997 until the end of follow-up. AS was defined as a diagnosis code of 424B (includes aortic regurgitation) or 746D (*ICD-9*) and I35.0, I35.2, or Q23.0 (*ICD-10*) as registered in the NPR.

Statistical Analysis

All Swedish siblings identified from the Multi-Generation Register were included in the analyses. Siblings were defined as 2 individuals sharing the same 2 biological parents. Cases were identified from both primary and secondary discharge diagnoses of AS in the NPR. Individuals without a sibling history of AS were used as reference. Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs) using Cox proportional hazards regression models. The proportional hazards assumption was confirmed by visual inspection of Kaplan–Meier curves (Figure I in the Data Supplement). Three different models were examined with adjustment for different covariates. The first analysis included adjustments for age and sex. The second model adjusted for age, sex, and family size. Family size was included because a higher number of siblings implies a higher risk that ≥1 of them is affected by AS. The fully adjusted model included age, sex, number of siblings, and comorbidities (hospital diagnosis of atrial fibrillation, hypertension, chronic obstructive pulmonary disease, obesity, diabetes mellitus, and coronary heart disease). Comorbidities were selected a priori and included known cardiovascular diseases associated with increased likelihood of echocardiographic examination and risk factors that have previously been shown to be associated with increased risk of AS.[12,26–28] Because each family will contribute multiple cases (proband [ascertained at separate time points for each afflicted sibling] and affected siblings), resulting in dependence of cases, we adjusted variance accordingly (1/[number of cases–number of ascertained families]) as described previously and further tested this in a Frailty model.[29]

Sensitivity Analyses

Several sensitivity analyses were included in the current article to try to stratify the results into different subtypes of AS and reduce bias. A sensitivity analysis excluding congenital AS, commonly used for BAV in the Swedish version of *ICD-10*, was performed to reduce the impact of BAV on our results. In an attempt to further evaluate the effect of BAV on our results, a sensitivity analysis stratified to only include patients aged ≥70 years was conducted because patients with BAV tend to be younger when they receive an AS diagnosis. Addition of Q23.1 (*ICD-10*), sometimes used to code for BAV, to the model was also explored separately in a sensitivity analysis. Outpatient diagnoses of AS between 2001 and 2010 were included in a separate analysis to capture patients diagnosed in an outpatient setting. The risk of having a brother and a sister was explored separately by sex in a Cox proportional hazards regression model.

The population attributable proportion for having a sibling with AS was calculated according to population attributable proportion=$P_c(RR_c-1)/(1+P_c[RR_c-1])$ where P_c is the prevalence of the exposure (sibling history) and RR_c is the relative risk of the exposure.[30] To evaluate potential inheritance models of AS, simple segregation analysis was also performed, using the Li–Mantel method.[31–33]

To evaluate the influence of a shared environmental burden, analysis of spousal history was also performed. People living at the same address with common children, in marriage, or people with registered partnership were considered as spouses. Risk estimates were calculated using Cox proportional hazards regression analysis as described above for sibling history and further stratified by sex of the index case.

A 2-sided *P* value of <0.05 were considered statistically significant. All statistical analyses were conducted in SAS, version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Sample Characteristics

A total of 6 117 263 siblings were identified, of which 51.2% were men and 48.8% were women (Table 1). Of those, 13 442 subjects were diagnosed with AS. The total number of families was 2 410 115 of which 13 111 families had ≥1 member diagnosed with AS. Men were more commonly diagnosed with AS than women (67.2% and 32.8% of cases, respectively). A U-shaped age distribution was observed in the identified cases, with a smaller peak in incidence during the first 10 years of life (9.9% of cases), followed by lower incidence in the second to fourth decade of life, and another peak in identified cases from the fifth decade of life and onward. A history of previous ischemic heart disease, atrial fibrillation, and hypertension was common in patients diagnosed with AS (23.6%, 20.2%, and 38.6%, respectively). Other comorbidities were also numerically more common in patients with AS cases compared with controls.

A sibling history of AS was rare in the general population, 0.5%. In patients diagnosed with AS, a sibling history was 10-fold more common than in the general population, although still only present in a small subset of AS cases (4.8%).

Sibling Risk of AS

The risk for AS was markedly higher in subjects with a sibling history of AS in a model adjusted for age and sex (HR, 4.18; 95% CI, 2.73–6.39), as compared with subjects without sibling history (Table 2). Further adjustments in models 2 and 3 resulted in only slightly declining risk estimates of 4.11 (95% CI, 2.68–6.30) and 3.41 (95% CI, 2.23–5.21), respectively. Using a Frailty model to adjust for variance did not significantly alter the results (model 3; HR, 3.23; 95% CI, 2.10–4.94). Individuals with ≥2 siblings with a history of AS had an exceptionally high risk of AS in the fully adjusted model (HR, 32.84; 95% CI, 20.47–65.17), but such sibships were rare (n=34 from 11 sibships; Table 3; Table I in

Table 1. Study Population and AS Cases

	Population		AS Cases	
	n	%	n	%
Population	6 117 263			
Subtype of events			13 442	
AS (I35.0)			7620	56.7
AS with AR (I35.2)			1836	13.7
Rheumatic AS (I06.0)			76	0.6
Rheumatic AS with AR (I06.2)			68	0.5
Congenital AS (Q23.0)			1166	8.7
Sex				
Men	3 131 437	51.2	9030	67.2
Women	2 985 826	48.8	4412	32.8
Age at diagnosis, y				
<20			1335	9.9
20–29			324	2.4
30–39			455	3.4
40–49			965	7.2
50–59			2747	20.4
60–69			5195	38.6
70+			2421	18.0
Birth year				
1932–1941	427 786	7.0	5736	42.7
1942–1951	857 926	14.0	3981	29.6
1952–1961	815 304	13.3	1392	10.4
1962–1971	896 426	14.7	581	4.3
1972–1981	786 629	12.9	344	2.6
1982+	2 333 192	38.1	1408	10.5
Family size (children)				
2	3 054 368	49.9	5677	42.2
3	1 863 846	30.5	3801	28.3
4	693 036	11.3	1976	14.7
≥5	506 013	8.3	1988	14.8
COPD				
No	5 862 536	95.8	12 191	90.7
Yes	254 727	4.2	1251	9.3
Diabetes mellitus				
No	5 974 903	97.7	11 313	84.2
Yes	142 360	2.3	2129	15.8
Obesity				
No	6 056 355	99.0	13 136	97.7
Yes	60 908	1.0	306	2.3
Hypertension				
No	5 849 636	95.6	8257	61.4

(*Continued*)

Table 1. Continued

	Population		AS Cases	
	n	%	n	%
Yes	267 627	4.4	5185	38.6
Atrial fibrillation				
No	6 036 879	98.7	10 732	79.8
Yes	80 384	1.3	2710	20.2
Coronary heart disease				
No	6 016 643	98.4	10 266	76.4
Yes	100 620	1.6	3176	23.6
Sibling history of AS				
Without sibling history	6 088 680	99.5	12 792	95.2
With sibling history	28 583	0.5	650	4.8

Clinical characteristics of the study population and AS cases, including cases diagnosed between 1997 and 2010. AR indicates aortic regurgitation; AS, aortic valvular stenosis; and COPD, chronic obstructive pulmonary disease.

the Data Supplement). The population attributable proportion for familial clustering of AS was calculated to 3.49%. Simple segregation analysis of families with at least 1 affected sibling showed a segregation ratio of 0.023 (95% CI, 0.021–0.025).

Spouse Risk of AS
To evaluate the influence of shared adult environment, we also analyzed the potential influence of a history of AS in spouses on AS. A fully adjusted model of spouse history of valvular disease and risk of subsequent AS is shown in Table 4. Spouse history of AS was associated with a modestly increased risk of AS, with a HR of 1.16 for a history of AS in a husband (95% CI, 1.05–1.28) and a HR of 1.18 for a history of AS in a wife (95% CI, 1.07–1.30).

Sensitivity Analyses
Cases of AS coded as congenital, which is likely to include cases of BAV, were excluded in a sensitivity analysis (n=1641; Table II in the Data Supplement). Exclusion of cases with congenital AS did not significantly change the results (HR, 3.58; 95% CI, 2.33–5.49) as shown in Table III in the Data Supplement. However, congenital cases with a sibling history were rare (n=30). The addition of congenital aortic insufficiency to the model did not substantially alter the risk estimates (HR, 3.58; 95% CI, 2.20–5.46).

The most common age of AS onset in siblings of index cases was 60 to 69 years. A higher HR was noted for siblings in the lowest age category, but there were few cases (HR, 9.61; n=17). Similar risk estimates were noticed for the older sibling age groups (≥40 years of age; Table IV in the Data Supplement). There was no correlation between family size and AS among siblings (Table I in the Data Supplement).

When patients diagnosed in an outpatient clinic between 2001 and 2010 were also included, the estimates remained essentially the same (HR, 3.68; 95% CI, 2.35–4.65). In the older patient category (>70 years of age), the risk estimates associated with a sibling history of AS were lower but remained highly significant (HR, 2.92; 95% CI, 1.77–4.82).

Table 2.   Risk of AS With Sibling History of AS

		Model 1		Model 2		Model 3	
	n	HR	95% CI	HR	95% CI	HR	95% CI
Sibling history of AS	650	4.18	2.73–6.39	4.11	2.68–6.30	3.41	2.23–5.21
Male sex		2.04	1.39–2.98	2.04	1.39–2.99	1.62	1.11–2.37
Birth year		0.94	0.66–1.33	0.94	0.66–1.33	0.96	0.68–1.35
Family size				1.02	0.71–1.45	1.01	0.71–1.44
Medical history							
COPD						1.74	1.17–2.61
Diabetes mellitus						1.55	1.05–2.30
Obesity						1.08	0.68–1.70
Hypertension						2.95	2.00–4.33
Atrial fibrillation						3.25	2.20–4.81
Coronary heart disease						2.99	2.03–4.41

Model 1: adjusted for sex and birth year. Model 2: adjusted for sex, birth year, and family size. Model 3: full model (adjustments in model 2 combined with comorbidities). AS indicates aortic valvular stenosis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; and n, number of AS cases.

There was no substantial difference between having a brother (HR, 3.47; 95% CI, 2.23–5.40) or sister (HR, 3.28; 95% CI, 2.02–5.32) with AS. The incidence estimates were similar across birth order for the siblings (26.1 per 100.000 person-years for the first-born sibling) and are shown in Table V in the Data Supplement.

Discussion

This nationwide register study of Swedish siblings indicates that AS can have a significant familial component. A strongly increased risk for AS was observed in subjects with a sibling with aortic valvular disease. The findings were robust and resulted in a 3.5-fold increased risk in the fully adjusted model, but the prevalence of a sibling history was low resulting in a population attributable proportion of only 3.5%. In contrast, spousal history of AS was only weakly associated with AS. Inclusion of patients diagnosed in an outpatient clinic, likely with less-severe disease, did not substantially change the estimates.

Sibling and Spousal AS Risk and the Pathogenesis of AS

Few studies have previously examined the familial contribution to AS, likely because few studies have had access to nationwide, nearly complete data. A familial aggregation has been described in a study of certain regions in western France,[18] but no systematic investigation of familial aggregation of AS in the general population has previously been undertaken to our knowledge. The strong association of AS with sibling AS observed in our study suggests a familial component to AS, and the weak association with spousal AS further indicates that shared adult environmental factors might contribute to the familial component of AS but to a lesser extent than genetic or epigenetic factors. There were no differences in risk estimates between having a brother or sister with the disease, consistent with an autosomal inheritance pattern.

The pathogenesis of AS has undergone transitions during the 20th century. At the onset of the 20th century, the most common cause of aortic valve disease was rheumatic fever, largely a disease affecting the young after a streptococcal infection.[34] Rheumatic fever is, however, uncommon in modern Sweden as recently described by our group[5] and unlikely to have influenced the results in our study. Immigration from countries where rheumatic fever remains endemic was also limited to Sweden during the study period. Some contribution can, however, not be entirely ruled out because the oldest individuals in this study were born before the era of widespread antibiotic treatment for streptococcal disease and the epidemiological transition. These individuals would likely share this environmental risk with their siblings, which imply that the familial risks for some of the oldest individuals may be explained by environmental rather than genetic factors.

Today, AS is a complex disease with a late onset in life, with the highest prevalence in subjects >70 years of age, characterized by lipid deposition and inflammation in the aortic valve, with progressive calcification.[1,2,8,9,35,36] The pathophysiological mechanisms of this calcific aortic valve disease are not fully understood but are thought to include high shear stress, inflammation, high levels of circulating lipids, and endothelial insults, similar to atherosclerotic disease.[37,38] Risk factors for AS are also similar to atherosclerotic disease and include sedentary lifestyle, obesity, dyslipidemia, diabetes mellitus, and

Table 3.   Risk of Aortic Stenosis With a History of Multiple Siblings With Aortic Stenosis

	n	HR	95% CI*
1 sibling†	616	3.26	2.13–7.58
≥2 siblings†	34	32.84	20.47–65.17

CI indicates confidence interval; HR, hazard ratio; and n, number of aortic stenosis cases.

*Adjusted for dependence between the sibling pairs.

†Full model, adjusted for sex, birth year, family size, and comorbidities.

Table 4.   Subsequent Risk of Aortic Stenosis for Spouses of Incident Cases

	n	HR	95% CI
Spouse history	407		
Wives		1.17	1.06–1.29
Husbands		1.13	1.03–1.25

CI indicates confidence interval; HR, hazard ratio; and n, number of aortic stenosis cases.

hypertension, which was also reflected by a high prevalence of previous ischemic heart disease in the AS cohort.[12,26–28] The finding of a strong association of sibling AS with AS risk in this study is unlikely to be fully explained by shared environmental factors because the risk estimates for the spouse analysis, which accounts for similar lifestyles in adulthood, showed substantially weaker associations with AS. However, such factors are known to have a modest heritable, polygenic component, which may contribute to the observed heritability of AS. A familial component has also been shown for a subset of AS cases with a congenital BAV, typically presenting at an earlier age than calcific valve disease.[19–21] BAV is relatively common, with prevalence estimates in the general population of 0.5% to 1.5% and a male predominance, similar to our results.[39–41] Previous studies of AS in the Swedish population have also shown a male predominance in this time period and a higher median age of diagnosis for women.[16] The later onset of AS in women, similar to other atherosclerotic cardiovascular manifestations, could account for part of the male predominance in the current study because only patients <78 years of age were included. However, the sensitivity analyses excluding cases with congenital AS, commonly used for BAV, did not change the results. Exclusion of patients <70 years of age did not impact the results substantially, indicating that the results reported are robust across the entire spectrum of AS because individuals with BAV generally have an earlier onset of disease than degenerative calcific AS. However, subjects with BAV represent a substantial proportion of patients with AS, and part of the risk associated with a sibling history of AS may reflect familial aggregation of BAV.

Genetic Background of AS

The genetic background of AS remains largely unknown. In simple segregation analysis, we observed a low segregation ratio consistent with a polygenic inheritance, in agreement with the current understanding of disease development.[32,42,43] The pathophysiological understanding of AS as described above is also consistent with that of a complex disease, influenced by a complex interaction between genes and environment. Genome-wide association studies have been successful in identifying genetic polymorphisms associated with complex traits and contributing to polygenic inheritance. Although of individually small effect, such polymorphisms in aggregate can explain a substantial proportion of disease risk. However, to robustly detect such small effect sizes, large sample sizes are also required. In a genome-wide association study of aortic valve calcification, lipoprotein(a) and low-density cholesterol have shown strong associations supporting the concept

of a causal role for lipoprotein metabolism in AS.[10,25] A smaller genome-wide association study of AS has also implicated calcium signaling pathways and the genes *RUNX2* and *CACNA1C*.[44]

The association of a genetic predisposition to increased levels of lipoprotein(a) and plasma lipids with the development of AS indicates a causal association.[10,25] However, the importance of lipid accumulation is likely most pronounced early in disease development, and as AS progresses, other mechanisms, such as fibrotic remodeling and osteoblastic transformation, seem to be more important.[37] This could also explain the negative trials of lipid-lowering therapy, mainly including patients with moderate-to-severe AS.[13–15]

We observed a strongly increased risk of AS in subjects with multiple affected siblings, potentially consistent with monogenic inheritance in a subset of cases alternatively a strong polygenic component in these families.[41] Not much is known about monogenic causes of AS, although mutations in the *NOTCH1* gene have been associated with BAV and could contribute to AS heritability in the small number of families with high risk of AS.[45,46] Additional molecular genetic studies are, however, warranted to better understand both the polygenic and monogenic forms of AS.

Clinical Implications

The current study implicates family history as a risk factor for AS. However, the risk increase was relatively modest, and a sibling history was rare in patients with AS (4.8%), which is why echocardiographic screening of subjects with a sibling history of AS in the general population seems unlikely to yield substantial clinical benefits. However, for patients with multiple siblings with AS, the risk estimates were considerably higher, and screening of such patients might be considered, especially for patients with additional risk factors.

Limitations

The register-based study design, although allowing population-wide coverage and excellent statistical power, limited access to information on the pathogenesis of AS in individual cases, as well as echocardiographic parameters and cardiovascular risk factors. However, in previous work based on review of patient records, we have described the validity of AS diagnoses in our nationwide registers to be high and typically to include both moderate and severe disease. It is possible that several subjects with a sibling history and less-severe AS were not adequately captured as cases in our analysis and that the current study, therefore, may underestimate the contribution of heritability to AS.

It is possible that relatives to individuals with a diagnosed valvular disorder could be expected to be more prone to seek medical attention and, therefore, more likely to be diagnosed with subclinical valvular disease. However, because this study is based on the hospital discharge diagnosis and omits diagnosis in a primary care setting, the diagnoses are likely to represent clinically relevant disease. This contention is also supported by the large difference between relative risk estimates for siblings and spouses, the latter category probably has just as strong influence on seeking patterns as siblings.

Conclusion

A sibling history of a hospital diagnosis of AS was strongly associated with AS, indicating a contribution of genetic predisposition for AS development. Spousal history of AS only conferred a slight risk increment, indicating a limited role for shared adult environment. Further studies are warranted to understand the detailed genetic architecture and pathways involved in AS development.

Disclosures

None.

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CLINICAL PERSPECTIVE

During the 20th century, aortic valvular stenosis transitioned from mainly a rheumatic disease to a progressive degenerative process similar to atherosclerosis. The disease commonly manifests late in life. Clinical risk factors include age, smoking, hypertension, and diabetes mellitus, and in addition, congenital malformations, most commonly with a bicuspid aortic valve, are important for the development of aortic valvular stenosis. Comprehensive studies investigating the heritability of aortic valvular stenosis are currently lacking. In the current study, nationwide Swedish registers were used to examine the familial aggregation of aortic valvular stenosis and the risk associated with having a sibling with aortic valvular stenosis calculated. The entire Swedish population ≤78 years of age was included. Our findings suggest that having a sibling with aortic valvular stenosis significantly increases the risk of being diagnosed with aortic valvular stenosis. The risk estimates far surpassed risk estimates for spouses of patients with aortic valvular stenosis. Having ≥2 siblings with aortic valvular stenosis was associated with an exceptionally high risk, but such families were uncommon. Our study provides novel data suggesting that despite the late onset of aortic valvular stenosis, a genetic predisposition may contribute to the development of aortic valvular stenosis. In addition to traditional cardiovascular risk factors, a family history of aortic valvular stenosis might warrant a higher level of suspicion and should be taken into consideration when evaluating patients for aortic valvular disease.

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SUPPLEMENTAL MATERIAL

Supplementary table 1. Number of children and the corresponding number of aortic stenosis cases.

Nr of children	Number of siblings with AS				
	1	**2**	**3**	**4**	**Total (N)** **Percentage of total AS cases**
2	5539 41.21 97.57	138 1.03 2.43	0 0.00 0.00	0 0.00 0.00	5677 42.23%
3	3618 26.92 95.19	180 1.34 4.74	3 0.02 0.08	0 0.00 0.00	3801 28.28%
4	1857 13.81 93.98	116 0.86 5.87	3 0.02 0.15	0 0.00 0.00	1976 14.70%
5	880 6.55 91.29	78 0.58 8.09	6 0.04 0.62	0 0.00 0.00	964 7.17%
6	441 3.28 91.88	36 0.27 7.50	3 0.02 0.63	0 0.00 0.00	480 3.57%
7	215 1.60 86.69	24 0.18 9.68	9 0.07 3.63	0 0.00 0.00	248 1.84%
8	113 0.84 79.02	26 0.19 18.18	0 0.00 0.00	4 0.03 2.80	143 1.06%
9	61 0.45 85.92	4 0.03 5.63	6 0.04 8.45	0 0.00 0.00	71 0.53%
10	42 0.31 91.30	4 0.03 8.70	0 0.00 0.00	0 0.00 0.00	46 0.34%
11	19 0.14 65.52	10 0.07 34.48	0 0.00 0.00	0 0.00 0.00	29 0.22%

12	4	0	0	0	4
	0.03	0.00	0.00	0.00	0.03%
	100.00	0.00	0.00	0.00	
13	2	0	0	0	2
	0.01	0.00	0.00	0.00	0.01%
	100.00	0.00	0.00	0.00	
14	1	0	0	0	1
	0.01	0.00	0.00	0.00	0.01%
	100.00	0.00	0.00	0.00	
Total	12792	616	30	4	13442
	95.16	4.58	0.22	0.03	100.00%

Supplementary Table 2. Number of AS cases by ICD-code.

	Events		Median	Mean age
	No.	%	age	
Total events	13442		61	55.2 ± 18.9
Aortic valvular stenosis (I35.0)	9103	67.7	64	61.8 ± 10.6
Aortic valvular stenosis with aortic regurgitation (I35.2)	2469	18.4	60	57.3 ± 12.8
Rheumatic aortic valvular stenosis (I06.0)	120	0.9	60	57.5 ± 10.4
Rheumatic aortic valvular stenosis with aortic regurgitation (I06.2)	109	0.8	58	54.7 ± 13.5
Congenital aortic valvular stenosis (Q23.0)	1641	12.2	12	15.3 ± 14.3

Supplementary table 3. Risk of aortic stenosis with a sibling history of AS, excluding congenital AS.

N	HR	95% CI
620	3.58	2.33 – 5.49

Adjusted for gender, birth year, and family size. Cases of congenital AS (ICD-10 Q230) were excluded.

Supplementary Table 4. Risk of AS with a sibling history of AS stratified by age.

Age at diagnosis	N	HR	95% CI
<20	17	9.61	4.14 - 22.34
20-39	6	1.91	0.60 - 6.07
40-49	23	2.47	1.15 - 5.32
50-59	122	3.15	1.85 - 5.36
60-69	314	3.12	1.97 - 4.96
≥70	169	3.04	1.84 - 5.03

Adjusted for gender, birth year, and family size, and comorbidities. AS: Aortic stenosis. N: number of AS cases.

Supplementary Table 5. Number of cases and incidence rate of AS by birth order

Birth order	Population		AS events		Incidence rate* (per 100 000 person years)
	No.	%	No.	%	
First	2410115	39.4	4967	37.0	26.1
Second	2410115	39.4	4870	36.2	25.9
Third	882931	14.4	2107	15.7	26.4
Fourth	261649	4.3	862	6.4	27.0
Fifth or later	152453	2.5	636	4.7	29.5
All	6117263	100.0	13442	100.0	26.2

*: Adjusted for European standardized population

Supplementary Figure 1. Kaplan-Meier curves for visual inspection of the proportional hazards assumption.