

# A population-based case-control study of the familial risk of abdominal aortic aneurysm

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**Background:** Several studies have reported a familial clustering of abdominal aortic aneurysm (AAA) supporting that AAA is an inheritable disease, but few population-based studies can be found. Possible gender differences regarding hereditary patterns have been reported.

**Objective:** The aim of this study was to investigate the risk of developing an AAA for first-degree relatives of patients with AAA in Sweden and compare them with matched controls and their relatives.

**Methods and Materials:** All persons (3183) born after 1932, diagnosed with AAA between 2001 and 2005, and a random selection of 15,943 age-, gender-, and region-matched controls were included. First-degree relatives of cases and controls were identified via the Multigeneration Register. Family history of AAA for cases and controls was assessed by linking the relatives to the Hospital Discharge Register and Cause of Death Register. The data were analyzed by conditional logistic regression.

**Results:** The overall relative risk of AAA associated with family history compared to no family history was 1.9 (95% confidence interval [CI] 1.6-2.2). Comorbidities were more common among the cases than the controls ( $P < .0001$ ) but the relative risks remained unchanged after adjustment for comorbidities. Stratification for absence or presence of comorbidities showed no significant difference between the two groups ( $P = .29$ ). The relative risk of AAA for first-degree relatives was similar for women and men ( $P = .22$  for gender differences), ie, the relative risk of AAA was not dependent on the gender of the index person.

**Conclusion:** In this nationwide survey, the relative risk of developing AAA for first-degree relatives to persons diagnosed with AAA was approximately doubled compared to persons with no family history. Neither the gender of the index person nor the first-degree relative influenced the risk of AAA. (*J Vasc Surg* 2009;49:47-51.)

Familial clustering of abdominal aortic aneurysm (AAA) was described more than 30 years ago.<sup>1</sup> Case series have reported increased familial risk for AAA and several studies have reported a high prevalence of AAA among siblings of AAA patients.<sup>2-4</sup> Case-control studies have shown an approximately four-fold increased risk being affected for first-degree relatives of AAA patients.<sup>5,6</sup> These studies are mostly based on consecutive patient series from one or few centers, and few population-based reports covering the subject can be found.

Possible gender differences regarding hereditary patterns have been reported, but the results from these studies are probably not possible to generalize.<sup>7,8</sup> Other important gender differences are known for AAA; men have a higher

prevalence and are younger at onset of disease compared to women.<sup>9,10</sup>

In order to perform a population-based case-control study, longitudinal data from nationwide registers is necessary. Sweden has a Multigeneration Register including first-degree relatives of persons born after 1931. This register, together with the Cause of Death Register and the In-patient Register, was utilized to perform a case-control study with the aim of investigating the risk to develop an AAA associated with a positive family history and possible gender differences.

## METHODS

**National registries.** All Swedish citizens have a unique 12-digit personal identification number, enabling identification of patients in national registries. The Swedish National Hospital Discharge Register, managed by the Swedish Board of Health and Welfare (NBHW), covers all information regarding public in-patient care. The Cause of Death Register is managed by the Centre for Epidemiology, NBHW, and covers data for cause and time of death for all deceased persons. The Multigeneration Register, managed by Statistics Sweden, contains linkages between children and parents and consists of persons in Sweden born after 1931 and their parents. The extraction of data was based on the diagnostic codes classified by the International Classification of Diseases (ICD) (Table I).

**Study population.** Cases ( $n = 3183$ ) were defined as all persons found in the Swedish National Hospital Discharge Register with a first admission under the diagnosis of AAA or an aortic aneurysm without a given localization

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**Table I.** Diagnostic codes classified by the International Classification of Diseases (ICD)

	ICD			
	7	8	9	10
AAA	451.00	441.20	441.3 441.4	I71.3 I71.4
Aortic aneurysm*	452	442	441.5 441.6	I71.8 I71.9
COPD	500-502	490-492	491.2 491.8 496	J44
IHD	420	410-414	410-414	I20-I25
Heart failure	431.10	428.99	428	I50
Hypertension	440-447	440-404	401-405	I10-I15

AAA, Abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease.

\*Without given localization.

(I71.3, I71.4, I71.8, or I71.9) between 2001 and 2005, and all persons deceased during the same period with the corresponding underlying or contributing cause of death that not was found in the hospital register. A random selection of 15,943 age-, gender-, calendar year-, and region-matched controls were identified from the Register of Total Population. The Swedish population was 8.9 million (50.5% women) in 2001 and 9.0 million (50.4% women) in 2005.

**Exposures.** First-degree relatives of cases and controls were identified via the Multigeneration Register. Family history of aortic aneurysm for cases and controls was assessed by linking the relatives to the Hospital Discharge Register and Cause of Death Register (for codes used see Table I). Comorbidity for cases and controls was assessed by the prevalence of admissions with selected diagnoses 5 years prior to the diagnosis date for the case and the corresponding period for the matched controls (for codes used see Table I).

**Statistics.** Crude comparisons of proportions were performed by  $\chi^2$  tests. Significance was defined as  $P < .05$ . The risk of AAA in relation to family history was estimated by means of conditional logistic regression and odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Risks associated with family history were assessed with respect to number of affected relatives and the gender of affected relatives. In stratified analyses with respect to the subjects' age, gender, and diagnosis the potential effect modification of these factors were investigated and tested by likelihood ratio tests.

Risks in relation to family history were adjusted for presence of comorbidity. The categorization of the comorbidity according to the different comorbidities alone and combinations of two, three, or four comorbidities was chosen due to the lack of multiplicative effects of the different comorbidities. We also performed an interaction analysis of the effect of family history among cases and control with and without any comorbidity; this interaction was tested by a likelihood ratio test. The study was approved by the Regional Ethics Committee.

**Table II.** Characteristics for cases and controls

Characteristics	Cases (n = 3183)	Controls (n = 15,943)	P
	No (%)	No (%)	
Gender			
Females	535 (16.8)	2679 (16.8)	.9951
Age			
<40	29 (0.9)	145 (0.9)	.999
41-49	54 (1.7)	269 (1.7)	
50-59	509 (16.0)	2531 (15.9)	
60-69	2031 (63.8)	10,196 (64.0)	
70-73	560 (17.6)	2802 (17.6)	
Family history			
Yes	268 (8.4)	743 (4.6)	<.0001
Number of affected relatives			
0	2915 (91.6)	15,200 (95.3)	<.0001
1	254 (8.0)	728 (4.6)	
2	12 (0.4)	14 (0.1)	
3	2 (0.1)	1 (0.01)	
Comorbidity			
No comorbid condition	2215 (69.6)	14,179 (88.9)	<.0001
IHD	297 (9.3)	652 (4.1)	
Hypertension	229 (7.2)	483 (3.0)	
Heart failure	50 (1.6)	88 (0.6)	
COPD	45 (1.4)	77 (0.5)	
Any 2 comorbidities	269 (8.5)	375 (2.4)	
Any 3 comorbidities	72 (2.3)	83 (0.5)	
All 4 comorbidities	6 (0.2)	6 (0.04)	
Diagnosis			
Rupture	840		
With family history	61 (7.3)		
Non-rupture	2343		
With family history	207 (8.8)		

IHD, Ischemic heart disease; COPD, chronic obstructive pulmonary disease.

## RESULTS

Among the 3183 cases with AAA, 479 were identified in the Cause of Death Register and 2704 in the Swedish National Hospital Discharge Register. A total of 840 cases were diagnosed with ruptured AAA. Baseline characteristics are listed in Table II.

A positive family history for AAA was significantly more common among cases than controls (8.4 vs 4.6%,  $P < .0001$ ). The cases had a significantly higher prevalence of comorbidities compared to the controls. The proportion of cases with family history was similar in patients with ruptured and non-ruptured AAA (Table II).

The overall relative risk of AAA associated with family history compared to no family history was approximately doubled (OR 1.9, 95% CI 1.6-2.2) (Table III). The risk increased further if more than one first-degree relative had AAA. The relative risks remained unchanged after adjustment for comorbidities (Table III).

In a logistic regression analysis stratified for absence or presence of comorbidities, there was no significant difference between the two groups, ie, the relative risk of AAA associated with family history was similar for cases suffering from comorbidities or not ( $P = .29$ ) (Table IV).

**Table III.** Relative risk of AAA

	Odds ratio (95% CI)	
	Unadjusted	Adjusted for comorbidity
Family history		
No	1.0 (ref)	1.0 (ref)
Yes	1.9 (1.6-2.2)	1.9 (1.6-2.2)
Number of affected relatives		
0	1.0 (ref)	1.0 (ref)
1	1.8 (1.6-2.1)	1.8 (1.6-2.1)
2	4.7 (2.1-10.2)	4.3 (1.9-9.8)
3	10.0 (0.9-110.3)	12.2 (1.1-137.0)

AAA, Abdominal aortic aneurysm; CI, confidence interval.

**Table IV.** Relative risk of AAA associated with family history stratified for comorbidity or not

Number of affected relatives	Odds ratio (95% CI)	
	Comorbidity = no	Comorbidity = yes
0	1.0 (ref)	1.0 (ref)
1	1.7 (1.5-2.1)	2.4 (1.7-3.3)
≥2	4.8 (2.0-11.5)	4.2 (0.8-21.8)

AAA, Abdominal aortic aneurysm; CI, confidence interval.

**Table V.** Relative risk of AAA for subgroups given family history (ref: no family history in the specific subgroups)

	Odds ratio (95% CI)	
	Unadjusted	Adjusted for comorbidity
Gender		
Male	1.8 (1.5-2.1)	1.9 (1.6-2.2)
Female	2.3 (1.6-3.3)	2.1 (1.5-3.1)
Age		
<49	2.7 (1.0-7.3)	2.4 (0.8-7.1)
50-64	1.8 (1.5-2.3)	1.9 (1.5-2.3)
65-73	1.9 (1.5-2.3)	1.9 (1.5-2.3)
Diagnosis		
Rupture	1.7 (1.3-2.4)	1.8 (1.3-2.4)
Non rupture	1.9 (1.6-2.3)	1.9 (1.6-2.3)

AAA, Abdominal aortic aneurysm; CI, confidence interval.

In a subgroup analysis, no significant gender difference in the relative risk of AAA associated with family history could be demonstrated ( $P = .22$  for differences between genders), ie, the relative risk of AAA was not dependent on the gender of the index person (Table V). No differences between age groups in the relative risk of AAA associated with family history were recorded ( $P = .75$ ) (Table V). Patients treated for rupture and non-rupture had similar relative risks of positive family history of AAA ( $P = .42$  for differences between rupture and non-rupture) (Table V).

There was a tendency towards a higher risk of being affected with AAA when having a male relative with AAA, compared to having a female relative ( $P = .07$ ) (Table VI).

**Table VI.** Relative risk of AAA given a certain gender of the index person and the first-degree relative (ref: no family history)

	Odds ratio (95% CI)	
	Female relative	Male relative
Male index person	1.6 (1.3-2.0)	2.1 (1.7-2.5)
Female index person	1.8 (1.1-2.9)	3.1 (1.9-5.0)

AAA, Abdominal aortic aneurysm; CI, confidence interval.

## DISCUSSION

It is of major importance for families and the society to clarify whether first-degree relatives of AAA patients have an increased risk to develop AAA compared to the general population. We found that a positive family history of AAA was associated with an approximately doubled risk of AAA. Comorbidities and gender of the index person did not modify the relative risk associated with family history.

Familial tendency of AAA was first described by Clifton in 1977.<sup>1</sup> Since then, several studies have reported a high prevalence of AAA among siblings of AAA patients, supporting that AAA is an inheritable disease.<sup>2-4</sup> In a case-control study of 98 AAA cases and 102 controls, a positive family history of AAA was associated with an increased risk of AAA (OR 4.77, 95% CI 1.26-18.1).<sup>5</sup> Similar risk rates were confirmed in a Finnish study of relatives of 150 AAA patients, but only 29% of the first-degree relatives were included in the study.<sup>6</sup> In a Canadian report, an approximately four-fold higher prevalence of AAA was found in siblings of 126 AAA patients compared to siblings of a control group.<sup>11</sup> The doubled risk of AAA associated with a positive family history in the present study confirms previously reported familial aggregation, but is lower than previously reported four-fold increase. Since AAA is a disease affecting the elderly, one concern with the present study is that the upper age limit of the included AAA cases was 73-years-old, but there were no age restrictions regarding the relatives. The present study covers the entire Swedish population; still misclassification is possible due to unknown relatives, eg, immigrants. The Swedish Multigeneration Register includes all persons born after 1931 and their parents; the coverage is 86% for known mothers and 83% for known fathers. The main effect of unknown relatives would be an underestimation of the effect of family history. There is also a risk of unreported cases with ruptured AAA due to low autopsy rates (14% in 2005) which is likely to add to the underestimation of the risk.

In a previous Swedish report by Hemminki regarding AAA from 1987 to 2001 using the same registers as in the present study, an increased standardized incidence ratio for siblings of AAA patients was found.<sup>12</sup> Their study design only included 71 affected sib-pairs between 0 and 69-years-old and included all types of aortic aneurysm.

In the present study, the risk of AAA associated with family history was neither influenced by the gender of the

index person nor the gender of the first-degree relative. This indicates that presence of family history should be taken into consideration regardless of gender when evaluating the risk to develop an AAA. It is, however, important to stress that our findings are based on index cases aged 73 years or younger. Since women develop AAA at an older age than men, a possible underestimation would be more pronounced for women. In two previous studies regarding the occurrence of AAA in relatives of AAA patients, the highest prevalence was found in brothers of female patients, but the differences were not significant.<sup>3,13</sup> A retrospective study on multiplex aneurysms without any control group reported a higher percentage of females among the affected relatives than among AAA probands.<sup>8</sup> In a prospective case-control study, there was an increased prominence of women in the familial AAA group.<sup>7</sup> However, the study group of 542 patients was from one center and the control group consisted of 500 spouses, non-blood relatives, and vascular patients without aneurysms which could have influenced the finding. Screening for AAA is cost effective for men above the age of 65, but this has not been shown to be the case for women. It is possible, and even likely, that the increased risk for women with a positive family history makes screening cost effective also for this group.

AAA is a multifactorial disease involving environmental and genetic risk factors. The present study design did not, however, address the genetic mechanisms. The increased risk for patients with more than one affected relative compared to only a single relative with AAA in our study supports that AAA is a multigenic disease. A recent study reported that a sequence variant on chromosome 9 (9p21) was associated with myocardial infarction, intracranial aneurysm, and AAA. The estimated degree of the effect differed and was most pronounced for AAA.<sup>14</sup> Kuivaniemi et al<sup>15</sup> performed a DNA linkage study for familial AAA in 233 families with more than one individual diagnosed with AAA. Linkage to chromosomes 19p13 and 4q31 were found, indicating that these regions could possess genetic risk factors for AAA. When investigating the manners of inheritance, they found that autosomal recessive inheritance was most common.

Patients with AAA often have manifestations of atherosclerotic disease, such as hypertension and coronary artery disease.<sup>9,16</sup> In the present study, AAA cases had more comorbidities which reflects that AAA patients often share the same risk factors as patients with other manifestations of cardiovascular disease. Since most AAAs are asymptomatic, the probability for detection will be influenced by contacts with healthcare providers. The occurrences of comorbidities obviously affect the frequency of such contacts, leading to an increasing number of diagnostic procedures. Regardless of the occurrence of comorbidities, the relative risk of AAA for first-degree relatives remained doubled in a stratified analysis. This emphasizes that family history is of major concern regardless if the person suffers from other cardiovascular diseases or not, as shown by others.<sup>5</sup>

In conclusion, in this nationwide survey the relative risk to develop AAA for first-degree relatives to persons diag-

nosed with AAA was doubled compared to persons with no family history. Neither the gender of the index person nor the first-degree relative influenced the risk of AAA.

## AUTHOR CONTRIBUTIONS

Conception and design: EL, FG, JS, RH  
 Analysis and interpretation: EL, FG, RH  
 Data collection: EL, FG  
 Writing the article: EL, RH  
 Critical revision of the article: EL, FG, JS, RH  
 Final approval of the article: EL, FG, JS, RH  
 Statistical analysis: EL, FG  
 Obtained funding: JS, RH  
 Overall responsibility: RH

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## DISCUSSION

**Dr Matthew Mell** (Madison, Wis). Could you speculate on the influence of smoking in your patient cohort and whether it may have acted as a confounding variable if a family smoking history was more prevalent?

**Dr Hultgren.** Well, that's impossible to say, since it's a register-based study. Looking at the comorbid conditions, you get a hint that probably smoking prevalence is much higher in the case group than in the control group. It's well known that smoking habits as well as dietary habits is inherited too through a social pattern. So probably it is much more prevalent in the case group.

**Dr Louis Nguyen** (Boston, Mass). I have a question regarding aneurysm screening in Sweden, because I am concerned that the likelihood for detection of AAA is different in your case group versus control group. A patient with a known aneurysm will more likely be told to have his relatives checked for an aneurysm as well. This scenario would then produce a higher incidence of relatives with AAA. For patients with no known AAA, their relatives would not have any reason to be screened unless there was a broad program in place. Can you tell us if AAA screening is routine and widespread in Sweden? Also, could you comment on whether or not the likelihood for detection of aneurysms in the relatives of your two groups was equivalent?

**Dr Hultgren.** Yes, I think that's an important point, and we've discussed that quite a lot. But we think at least by adjusting for the comorbid conditions you get rid of some of the problem

with over-diagnosing comorbid patients. Maybe it isn't that bad that we actually do screen first-degree relatives more, because they are probably at a much higher risk, so maybe that's actually quite motivated.

**Dr J. Black** (Baltimore, Md). Did you look at the age of presentation of the index cases with aneurysms and the number of affected relatives? The implication being that younger patients with more affected relatives might have a genetic syndrome and would prompt referral. Do you have that data available within the set?

**Dr Hultgren.** In the analysis of subgroups, we did get a higher odds ratio (OR) for younger patients having a higher risk for the first-degree relative, it didn't become significant compared to the OR of 1.8 in the older age groups. In the analysis of the thoracic patients, younger age was a higher risk to develop disease than in the AAA group.

**Dr K.W. Johnston** (Toronto, Ontario, Canada). What genetic testing do you consider doing in a patient with a positive family history of aneurysm to try and determine if they do indeed have an increased risk?

**Dr Hultgren.** Well, there have been some studies internationally looking at genes and genetic pathways, and nobody has really succeeded in finding one or two especially important genes. We will start a national screening program in a couple of years, and we are going to do a genetic screening based on that, let me come back in 3 years and I'll tell you more about it.