From Department of Clinical Science and Education, Södersjukhuset
Karolinska Institutet, Stockholm, Sweden

SCREENING FOR
ABDOMINAL AORTIC ANEURYSMS

Anneli Linné

Stockholm 2014

Life is like riding a bicycle. To keep your balance you must keep moving.
Albert Einstein

To Clara, Frida, William and Göran

Dept of Clinical Science and Education, Södersjukhuset,
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Screening for
Abdominal Aortic Aneurysms

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av
Anneli Linné
Specialistläkare, kirurgi

Huvudhandledare:
Docent Rebecka Hultgren
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Bihandledare:
Med. Dr. David Lindström
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Docent Sefan Rosfors
Karolinska Institutet
Inst för klinisk forskning och utbildning
Södersjukhuset

Fakultetsopponent:
Professor Jes Lindholt
Odense University Hospital
Dept of Cardiothoracic and Vascular surgery

Betygsnämnd:
Professor Toste Länne
Linköpings Universitet
Kardiovaskulär medicin

Professor Anna Martling
Karolinska Institutet
Institutionen för molekylär medicin och
kirurgi

Docent Jan Holst
Lunds Universitet,
Kärlcentrum Malmö

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Anneli Linné

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1. ABSTRACT

Abdominal Aortic Aneurysm (AAA) is a common disease with a prevalence of 1.5-2.0% in 65-year old men in Sweden. The risk of having AAA is increased with smoking, high age, family history of AAA and cardiovascular disease. Women have a lower prevalence (0.5%) and develop AAA later in life. An AAA seldom gives any symptom prior to rupture. Untreated rupture is associated with 100% mortality, while surgically treated rupture is associated with 25-70% mortality. Prophylactic surgery is associated with a relatively low risk (30-day mortality of 1-3%). Commonly, prophylactic surgery is offered at size 5.5 cm in men and 5.0 cm in women. As a result of randomized trials showing a benefit in terms of AAA-related mortality and all cause mortality, screening of 65-year old men have been implemented in Sweden. If a high proportion of invited persons chose not to participate in as creening programs, this will affect the positive effects of a screening program. Efforts to better understand and thereby to improve the participation rate should be made. This thesis is focused on different aspects of screening for AAA.

In the first and second studies we investigated siblings to AAA-patients in two different regions in Sweden. We examined 150 siblings in mid-Sweden (Stockholm) and 379 siblings in north Sweden (Norrbotten). In both regions a prevalence of 17% in brothers and 6% in sisters was found, strikingly high numbers as compared to the general population. We did not detect regional differences in prevalence. Further analysis of the 53 siblings found with AAA revealed that 32% had a large AAA and 16% had a large AAA before the age 65. Organized screening of both male and female siblings is motivated since the population-based screening is not sufficient for all of them.

The third study investigated reasons for non-participation in the population based AAA-screening program in Stockholm County. The individual socioeconomic- and health-status of 24319 men invited to screening was investigated and compared between participants and non-participants in screening. The risk of non-participation is increased with low income, low education, marital status single, immigrants and persons with long travel distance to examination-centre. The non-participants had a higher proportion of co-existing diseases. We concluded that immigrants and people with long travel-distance should be targeted in further attempts to improve screening-participation.

The fourth study concerns men with screening-detected AAA and their outcome when treated with prophylactic surgery. We compared all available treated screening-detected men in Sweden (n=350) to age matched, non screening-detected controls. There was no differences in comorbid conditions between the groups but open repair was used more frequently than EVAR in patients with screening-detected AAA´s than in non-screening-detected controls (56% vs 45%).
In terms of outcome, a lower 90-day mortality in screening-detected men was found, but no difference in 30-day or 1-year mortality. The overall 30-day mortality in all 700 men was very low at 1%. This gives further support to national screening programs for the detection of AAA´s in men.
Efforts should be made to find AAA's with improved screening of siblings and groups with low participation-rates in the screening programs.

Anneli Linné

SVENSK SAMMANFATTNING

Att finna pulsåderbråck innan de brister

Bukaortaaneurysm (BAA) är en lokal utvidgning av pulsådern i buken. Sjukdomen är relativt vanlig och förekommer hos ca 1.5% av 65-åriga män i Sverige. Ett litet BAA leder vanligen inte till några symtom men med ökad storlek finns en ökad risk för bristning, sk ruptur. Vid ruptur av ett BAA är dödligheten hos dem som inte kommer till sjukhus 100%. Bland dem som hinner till sjukhus och genomgår akut kirurgi är den kortsiktiga dödligheten 25-50%. Förebyggande operation erbjuds patienter med BAA som uppnått sådan storlek att risk för ruptur föreligger, vanligen 5,5 cm hos män, 5,0 cm hos kvinnor. Förebyggande kirurgi är liksom all större kärlkirurgi förenat med risk för blödningskomplikationer, hjärtinfarkt, blodpropp och infektioner. Den kortsiktiga dödligheten vid ett sådant förebyggande ingrepp var i Sverige 2012 1.7%. Eftersom sjukdomen BAA har hög dödlighet vid ruptur samtidigt som förebyggande kirurgi är förenat med låg dödlighet finns anledning att sträva efter att upptäcka ett BAA innan det brister. Screening för BAA startade i Sverige 2006 och erbjuds nu till 65-åriga män i alla landsting utom ett. I Stockholm startade screeningen 2010. Screeningen utförs med hjälp av ultraljud över buken, en metod som är smärtfri och tillförlitlig. Kvinnor har betydligt lägre risk för sjukdomen och inbjuds därför inte till screening.

Denna avhandling handlar om resultaten av screening, både ur perspektivet deltagande/icke deltagande i screening och hur det går för dem som screenats när de genomgår profylaktisk kirurgi. Den handlar också om syskon till BAA-patienter, en grupp kvinnor och män som har betydligt större risk för BAA än den övriga befolkningen.

Studie I. Vi undersökte 150 syskon (<80 år) i Stockholm och med ultraljud och konstaterade att 6% av systrarna och 17% av bröderna hade BAA. BAA är mycket vanligare hos syskon än hos befolkningen i övrigt i Sverige, och inga regionala skillnader i hereditet kunde påvisas.

Studie II. Syftet med denna studie var att undersöka om andelen syskon med BAA i Norrbotten hade högre prevalens BAA än syskonen i Stockholm. Bakgrunden var den att andelen personer med BAA i befolkningen i Norrbotten är högre och det diskuteras ibland om detta beror på stark ärftlighet. 379 syskon undersöktes, inga skillnader i förekomst av BAA hos syskon i Norrbotten jämfört med Stockholm påvisades, men vi fann att patienter med BAA i Norrbotten hade fler syskon än de i Stockholm. Åldrarna för de syskon som har BAA undersöktes fanns tillgängligt i 45 fall och vi fann att 16 (36%) av syskonen med AAA var 65 år eller yngre. Det fanns 16 syskon som hade ett AAA >5 cm eller var opererade. Av de 16 med stort AAA var 8 (50%) 65 år eller yngre. Med ledning åldrarna hos de screeningupptäckta föreslår vi 50 som en säker ålder för screening av bröder, 55 för systrar.

Studie III. Syftet med denna studie var att finna faktorer som påverkar deltagandet i screeningen. I Stockholm startade screeningen av 65-åriga män 2010. Vi gjorde utdrag ur svenska hälsoregister för de 24319 som inbjudits till screening, fördelat på deltagare och icke-deltagare. Deltagandet var 78 %. Deltagandet var lägre hos de som hade låg inkomst,

låg utbildningsnivå, var ogifta och har lång resväg till undersökningen. Invandare deltog i mindre omfattning än svenskar. Invandrare som varit i Sverige i mindre än 5 år som hade det lägsta deltagandet av alla. Vi kom fram till att det är motiverat att undersöka om erbjudande av screening närmare hemmet och kallelser på flera olika språk ökar deltagandet i dessa grupper.

Studie IV. Syftet med studie IV var att undersöka resultaten efter förebyggande kirurgi hos män med BAA upptäckt via screening jämfört med jämnåriga kontroller (med BAA som inte upptäckts via screening). Bakgrunden var att det i Sverige finns diskussioner om huruvida män med screeningupptäckta BAA är friskare och skall erbjudas annan förebyggande behandling än män med BAA som inte upptäckts via screening. Inga skillnader i sjuklighet före kirurgi i de två grupperna återfanns. Överlevnaden efter kirurgi var mycket god hos båda grupperna (1.1% 30 dagars mortalitet). Överlevnaden var något bättre för screeningupptäckta BAA-patienter 90 dagar efter kirurgi, men inte vid 30 dagar och 1 år efter kirurgi. Vi fann vidare att män med screeningupptäckta BAA i större omfattning behandlas med öppen operation jämfört med icke-screeningupptäckta (56% vs 45%).

Vi har kunnat påvisa att de postoperativa resultaten på screenade män är mycket goda, därmed finns all anledning att fortsätta verka för att finna patienter med asymtomatiskt BAA. I strävan att finna pulsåderbråck innan de brister behöver screeningen förbättras för förstagradsläktningar till BAA patienter. Vi behöver även göra fortsatta insatser för att öka deltagandet i screening i de grupper där deltagandet är lågt.

LIST OF PUBLICATIONS

This thesis is based on the following studies, referred to in the text by their Roman numbers

I.   **High prevalence of abdominal aortic aneurysms in brothers and sisters of patients despite a low prevalence in the population**

Anneli Linné, David Lindström, Rebecka Hultgren

J Vasc Surg. 2012 Aug;56(2):305-10

II. **Screening of Siblings to patients with Abdominal Aortic Aneurysms in Sweden**

Anneli Linné, Johan Forsberg, Karin Leander, Ester Ideskog, David Lindström, Rebecka Hultgren

Submitted

III. **Reasons for non-participation in population-based abdominal aortic aneurysm screening**

Anneli Linné, Karin Leander, David Lindström, Sven Törnberg, Rebecka Hultgren

Br J Surg. 2014 Apr;101(5):481-7

IV. **Low postoperative mortality after surgery on patients with screening-detected abdominal aortic aneurysms: A Swedvasc registry study.**

Anneli Linné*, Kristian Smidfelt*, Marcus Langenskiöld, Rebecka Hultgren, Joakim Nordanstig, Björn Kragsterman, David Lindström
*Equally contributed

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Anneli Linné

ABBREVIATIONS

AAA   Abdominal Aortic Aneurysm

ESVS   European Society of Vascular surgery

EVAR   EndoVascular Aortic Repair (percutaneuos aortic repair)

FDR   First degree relative

MRI   magnetic resonance imaging

NBHW   National Board of Health and Welfare

OR   Open Repair (open aortic surgery)

rAAA   Ruptured Abdominal Aortic Aneurysm

SVS   Society of Vascular Surgery

Anneli Linné

1. BACKGROUND

1.1 General aspects of Abdominal Aortic Aneurysm

An Abdominal Aortic Aneurysm (AAA) is a pathological widening of the abdominal aorta. The most important risk-factors for developing an AAA are high age, male gender, smoking, family history of AAA and Caucasian ethnicity. A true aneurysm is a widening with all three of the layers (intima, media and adventitia) of the vascular wall intact, as opposed to a false aneurysm where none of the layers are intact. A false aneurysm, or pseudoaneurysm is most often caused by penetrating trauma, accidental or associated with medical procedures (i.e. angiography) and will not be described further in this thesis.

The first historical recordings of treating the disease AAA is from the 2nd century AD when the Greek surgeon Antilles was the first to attempt surgical treatment with proximal and distal ligation of the aneurysm.[1, 2] The first successful surgical treatment of AAA was a ligation by dr Matas, which was reported in 1923.[1]
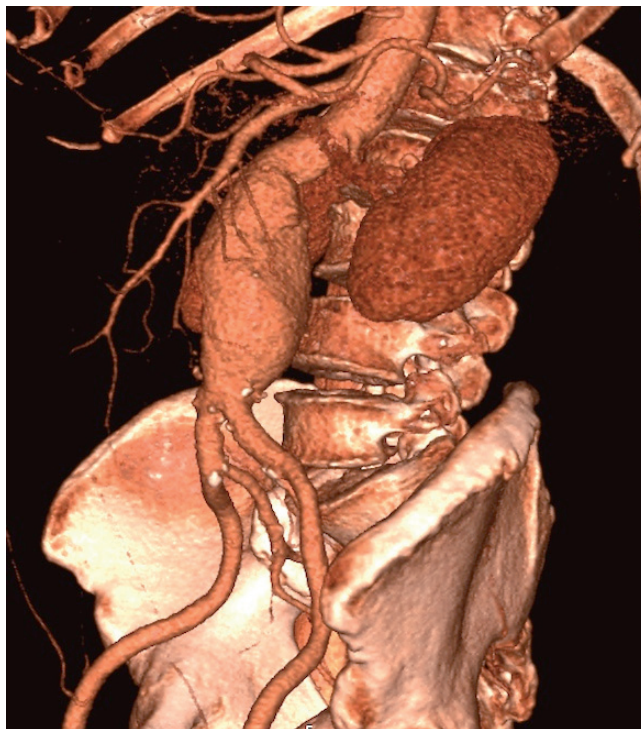
Definitions

The size of a normal aorta varies with body surface area, gender and age.[3, 4] There is more than one definition of an AAA, the most commonly used is an anteroposterior infrarenal diameter of ≥30 mm in men. This definition is used for screening-purposes in Sweden and Great Britain among others.[5, 6] Until 2009 the definition used in Stockholm, Sweden, was the same for men and women but after Wanhainens publication 2008, strengthened by data from the Tromsö study, the clinical definition was changed to 27 mm in women.[7, 8]

Another popular definition of an AAA is an increase in diameter ≥1.5 times the normal aorta.[9] This definition is probably more scientifically correct since it allows for adjustment of natural differences in aortic size (i.e a person with a large body is likely to have a larger aorta), which may vary greatly between individuals and genders. This definition is however less used in clinical practice since it requires information about the size of the "normal" aorta, information that is often not readily available. It is often hard to tell where the normal aorta ends and the pathological dilatation starts. An Italian research group has suggested that a correlation between the ultrasound aortic diameter to the wrist circumference would be more relevant.[10] Many groups worldwide are aiming at finding better definitions of AAA which can be especially important for subgroups, such as women.

Pathophysiology
The arterial wall has three layers: tunica intima, media and adventitia. The innermost layer, tunica intima, consists of endothelial cells. The medial layer consists of smooth muscle cells, elastin- and collagen-fibers. In large arteries like the aorta and its major branches the medial wall has a high content of elastic fibers. The adventitia consists of connective tissue.[11]

The formation of an aneurysm is a complex process in which all steps are not known. In the aortic aneurysmatic wall a degradation of extracellular matrix (elastin and collagen) is evident.[12, 13] Degradation is likely due to activation of degrading enzymes, matrix metalloproteinases (MMP's) emerging from smooth muscle cells. Especially MMP9 has been pointed out in this process.[14] The loss of elastin and collagen leads to weakening of the arterial wall and aneurysm formation.[15] There is also evidence of an inflammatory process with transmural infiltration of lymphocytes and macrophages; possibly activating the MMP's to start the degrading process.[13] The trigger for the entire process is not known and is likely to be multifactorial.[16] A genetic component is probable since AAA is more common in first-degree relatives.[17, 18] Recently some additional triggers that have been suggested in non-mycotic AAA's are different microorganisms i.e. H Pylori, Chlamydia, Mycoplasma pneumonie, Borrelia Burgdorferi.[19-22] It what way smoking, age and gender contribute to this process is not known. Biomechanical wall-stress is shown to be involved in aneurysm formation as well as progression of disease and risk of rupture.[23-25]

Genetics
Whether the increased risk for AAA in first-degree relatives is due to genetic heritability or tendency towards homogenous risk-pattern within families (i.e. increased risk of smoking if you have a smoking parent) is hard to establish. Wahlgren et al published convincing evidence for genetic heritability deduced from investigating mono- and dizygotic twins in Sweden.[26]

Despite admirable efforts no single gene has been identified as responsible for development of AAA. Genomic wide associations have identified at least three important genetic markers associated with an increased risk of AAA located within the genes for DAB2 interacting protein (DAB2IP) and low-density lipoprotein receptor-related protein 1 (LRP1). In addition, a marker on chromosome 9p21 that is associated with increased risk of cardiovascular disease including AAA has been found.[27] Also, a single nucleotid polymorphism (SNP) suggested to increase matrix metalloproteinase 3 (MMP3)

-expression could be a moderate risk factor for AAA.[14] An "epigenetic" background to development of AAA is suggested, meaning a combination of genetic and environmental factors.[28] This area of research is rapidly expanding and the results will be interesting to follow.

1.2 Diagnostic methods

There are four common ways to diagnose an AAA: Palpation, Ultrasound, CT-scan, and MRI.

The ultrasound is painless, quick and does not expose the patient to radiation. It is, however, depending on the operator of the ultrasound-machine. Trained operators have an intraobserver repeatability in measurements of 1-4.4mm in studies with standardized methods but as high as 10.4 mm's inter-observer reproducibility in some studies.[29, 30] Less than 5 mm variations in measurement are considered acceptable.[29] One of the advantages with ultrasound is the possibility to visualize the variation in aortic width in different cardiac cycles, also called the pulsewave mechanism (PWM). The change in aortic size varies on average 1.94 mm (range 0-4.7) between systole and diastole, a fact not possible to visualize (and often neglected) with either standard CT- or MRI-imaging techniques.[2, 31] When PWM was taken into account in a recent study the inter-observer reproducibility was within +-3 mm.[31] Measurement in peak-systole is recommended. In some recent studies the focus is to ameliorate growth of AAAs. In these studies detecting small differences in size is crucial and controlling for PWM could be important.

Obese patients can be difficult and sometimes even impossible to examine with ultrasound.

The 3D CT-scan is by many considered "the gold standard" and has the advantage of producing series of images that can be reconstructed. The CT-scan does expose the patient to a certain amount of radiation, though in the elderly cohort of AAA-patients this is unlikely to be of clinical relevance. The CT-scan, if carried out without Iodine-contrast, must be considered safe. CT-scan is, in hospitals in Sweden, slightly more expensive than ultrasound. A common clinical problem with CT-scans, if analyzed by non-specialized radiologists, is the failure to make 3-D reconstructions. In non-3D axial CT the aorta is often sliced on the oblique and the size potentially overestimated. The lack of information regarding in which of the cardiac cycles the images were collected is a limitation in most commonly used CT-scanner but technical development has solved this issue with the introduction of dynamic CT-scanner.[32]

MRI is a safe technique if all contraindications are respected (IUD, Pacemaker, Intracerebral clips and more) but much more expensive and less available in most centers and therefore not the method of choice when screening for AAA.

Ultrasound measurements

With the introduction of screening for AAA came the need for standardized methods of measuring the aorta with ultrasound. In present studies attempting to ameliorate the growth of AAA's there is a need for measurements to be as exact as possible. The issue of different techniques has been addressed in Sweden and there is now a nation-wide standard used. However, on an international basis the three methods are still used and there is every reason to be observant to this fact when interpreting study results.

What anatomical structure the echoes in an ultrasound image really corresponds to has been described.[33, 34] The below written regarding anatomical structures is a slight simplification of reality.

Outer To Outer (OTO)

In this method the aorta is measured including the anterior wall and the posterior wall, adventitia to adventitia. This is now considered the gold standard ultrasound method in the international arena.[2, 35] Used in UK-sat trial and in the ongoing UK-screening among others. [36]

Leading Edge to Leading Edge (LELE)

In this method the aorta is measured from the beginning of the anterior wall (adventitia) to the beginning of the posterior wall (intima-media complex). Used as standard technique in population-based screening in Sweden.[37, 38]

Inner to Inner (ITI)

In this method the aortic diameter is measured from intima to intima. Used in MASS-trial and Glochestershire trial. [39]

Table I. Variations in aortic diameter using different measurement-techniques.

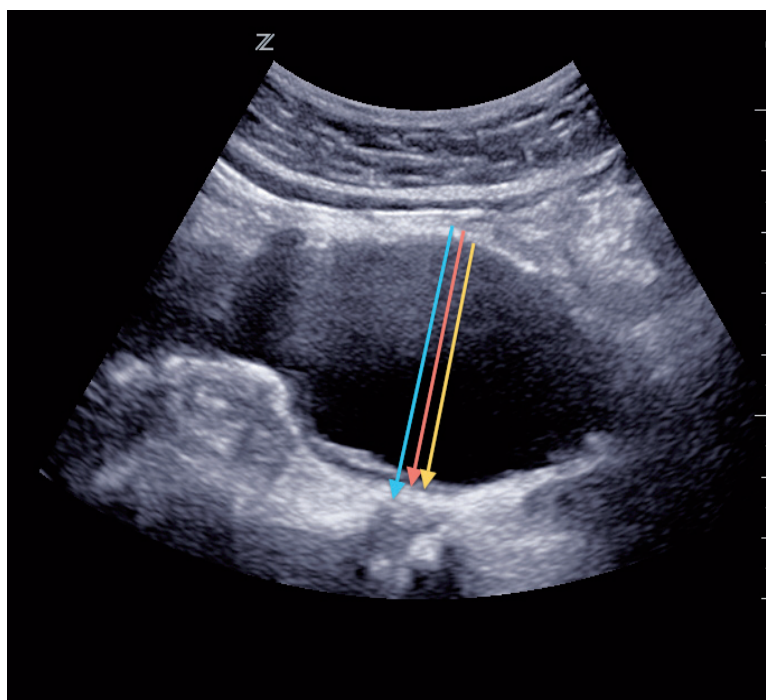| Diagnostic method	Approximate difference from CT 3D
CT without 3D	(+) 5 mm[40]
Ultrasound inner to inner	(-) 4-9 mm[41, 42]
Ultrasound outer to outer	(-) 0-1 mm[40, 42]
Ultrasound Leadning Edge to Leading Edge	(-) 2 mm[42, 43]

FIg II. *Different approaches to measure aortic diameter with ultrasound.*
Blue OTO, Red LELE, Yellow ITI

1.3 Epidemiology

AAA is more commonly found in elderly, in men, Caucasians, persons with other atherosclerotic diseases and in persons with a first-degree relative with AAA.
Smoker have an increased risk to develop the disease, but diabetics have lower.
The prevalence of AAA seems to be decreasing in many parts of the world but not all. It is likely that reduced smoking plays a major role in this.[44-46]
There are four major randomized screening trials: The Chichester-trial[47], The Multicenter Aneurysm Screening Study (MASS)[39], The Viborg-trial[48] and The Western Australia-trial[49]. The prevalence in these studies varied between 4-7.6% in men. Current knowledge of AAA's a to a high extent based on these studies, but also on more recent screening-materials who show a lower prevalence.[6, 37, 44] An overview of a selection of large screening-reports is shown in table II.

Table II. Large screeningreports and prevalence of AAA.

Study	Region	Age	Gender	Participants	Prevalence	Year data
UK NAASP[6]	UK	65	male	107 000	1.5%	2011-2012
Linné et al 2014[50]	Sweden, Stockholm	65	male	18 876	1.5%	2010-2012
Wahnhainen 2010[5]	Sweden, Uppsala	65	male	6 180	1.7%	2006-2010
Svensjö et al, 2012[51]	Sweden, Dalarna and Uppsala	70	female	5 812	0,4%	2007-2009
Scott et al 2002[52]	Chichester, United Kingdom	65-80	female	4 682	1.3%	1988-90
Scott et al 1995[47]	Chichester, United Kingdom	65-80	male	5 394	7.6%	1988-90
Lindholt et al 2002[53]	Denmark, Viborg	65-73	male	9 620	4.0%	1994-98
Norman et al[49]	Western Australia	65-74	male	12 203	6.1%	1996-98
Kim et al[54]	MASS UK	65-74	male	27 147	4.9%	1997-99
Palombo et al[55]	Italy, Genoa	>65	Male female	8 234	10.8% 1.1%	2007-2009
Pleumeekes et al[56]	Netherlands, Rotterdam	>55	male female	5 419	4.1%* 0.7%*	1994-95
Singh et al[57]	Norway Tromsö	55-74	male female	6 386	8.9% 2.2%	1994-95

* >35 mm or >50% increase in diameter

Gender differences

The prevalence of AAA is higher in males, with a male to female ratio internationally reported to be 5:1. The number of patients diagnosed with AAA and treated with in-hospital care in Sweden is shown in table III. The male to female ratio in Sweden is closer to 3:1 when in-hospital care in considered. Since women are older when diagnosed, and have more concurrent diseases it is not hard to understand that they less often are offered prophylactic surgery.[58] It is possible that women's more complex aortic neck-anatomy is the reason why they less often are offered surgery for rAAA, even when adjusted for age.[59] Women also have AAA's that grow faster, have higher risk of rupture and worse outcome after surgery.[58]

Table III. Number of patients treated in hospitals with diagnos AAA.

Gender	1998	2000	2002	2004	2006	2008	2010	2012
% Women	31%	33%	34%	35%	37%	37%	36%	35%
All	2 049	2 134	2 190	2 267	2 328	2 428	2 668	2 527

Number of patients treated in hospitals 1998-2012, Age 50+[60]

Heridity

The increased risk for first-degree relatives to AAA patients to also develop AAA has been published in several reports[61-70] with resulting prevalence rates ranging from 3-19%. The wide range is likely due to differences is study design, but also regional differences in prevalence. Although the increased risk for AAA in first degree relatives is well known among vascular surgeons, it is uncertain if this knowledge about sisters and brothers to AAA patients leads to screening of relatives. The prevalence of AAA in the general population seems to be declining but if this is true for prevalence in siblings is unclear. The possibilty that sibling-screening could be an underused tool was motivation for study I and II.

The best age at which to screen siblings

The recommendation regarding at what age the first-degree relatives (FDR) should be screened is scarce, although the European Society of Vascular Surgery (ESVS) includes a recommendation for the FDR over the age 50.[35] Previously published studies based on ultrasound screening of 49-300 siblings report ages 49-87 of siblings found with AAA, although some studies have not included siblings <50 years of age (table IV).

Brothers and sons in Sweden are likely to have their aneurysm detected at the age of 65 in the population-based screening but more data are needed to decide if detection at this age is sufficient for FDR or if screening at an earlier age is necessary to avoid ruptures. Because of lower prevalence and later development of disease women are generally not included in population-based screening in Europe.

Table IV. Ultrasound screening studies reporting ages of siblings at detection

Author	Number examined	Frequency of aneurysm	Cases	Age of siblings found with AAA
Sakalihasan (-14)[17]	186	13% FDR	25	<50-87*
Badger (-07)[62]	300	3% FDR	10	67-75
Rossaak (-01)[64]	49	19%	4	No AAA<55
Salo (-99)[65]	238	5%	11	50-78
van der Graaf (-98)[71]	210	12% FDR	26	50-80+**
Jaakola (-96)[72]	123	4.1%	13	48-82***
Fritzgerald (-95)[73]	125	12%	15	57-78
Bengtsson (-89)[74]	87	15%	13****	49-73
Linné (Current studies I and II)	529	10%	53	50-80*****

FDR= First degree relatives, not only siblings
*One son of AAA-patient reported to be less than 50, age not stated.
**Did not include siblings under 50.
*** One brother 48 y old.
**** Dilatations, not all >30 mm in men
*****Siblings < 80 included

Regional variations in Sweden

Sweden has latitudes ranging from North 55° to North 69°. People living in the North of Sweden experience quite different physical life-conditions regarding temperature (January average -16°C in Norrbotten, +2°C in Stockholm) and average hours of daylight (0 in Jan to 24 in June in Norrbotten, 4 to 20 in Stockholm). There are reports about large regional differences in cardiovascular disease over latitudes in Sweden.[75] Among others, the frequency of Abdominal Aortic Aneurysm (AAA) in the general population is higher in the north region of Sweden compared to the south with a 38% higher incidence for AAA in men.[76] Smoking is as common in the north and should subsequently not be responsible for the increased risk.[77] It has been shown that inhabitants of the North have higher levels of Cholesterol compared to inhabitants of South (Gothenburg).[78] Also, low levels of Vitamin D have recently been suggested as a possible explanation for increased risk of cardiovascular disease.[79, 80] A strong hereditary trait has also been suggested as an explanation to the regional differences in disease pattern[81]. Organized screening for AAA in siblings is currently not arranged in either region in Sweden.

1.4 Natural course, growth rate and risk of rupture

The natural course of an AAA is a gradual growth. The growth-rate increases with aneurysm size. The growth rate of an aneurysm is further increased in smokers, women and is decreased in diabetics.[82] The mean growth rate for a man with a 3.0 cm aneurysm is 1.28 mm/y, 3,5 cm aneurysm 1.86 mm/y, 4.0 cm aneurysm 2.44 mm/y, 4.5 cm aneurysm 3.02, 5.0 cm aneurysm 3.61 mm/y.[83]

Small aneurysms (<5.5 cm in men) have a low risk of rupture and the risk has recently been reported in a meta-analysis including over 15 000 patients.[83] As prophylactic surgery is associated with a 30-day mortality of 1-4% it is usually not offered until the risk of rupture exceeds the perioperative risk, normally at 5.5 cm in men. Two large trials have investigated the potential benefit of surgery on small aneurysm (4-5.5 cm), The UK small aneurysm trial (UK-SAT) and the ADAM trial. Neither showed a benefit of surgery compared to surveillance.[66, 84]

The risk of rupture in large aneurysms is less well investigated since the only possible ethical study-cohort consist if patients unfit for surgery, who possibly have a higher rupture risk than the average AAA-population. Also, the presented risk for rupture in large AAAs in the table below (table V) is based on studies published 1998 and 2002 Hence, it is possible that optimized medical treatment and decreased smoking have affected the rupture-rates since then. The risk of rupture is increased in women, smokers and patients with high blood pressure. The risk of rupture is decreased with the use of statins and in patients with diabetes.[39, 85-87]

Table V. Annual risk of rupture

Diameter, cm	3.0*	3.5	4.0	4.5	5.0	5.5**	6.0	7.0	8.0
Men %	0.05	0.1	0.2	0.3	0.6	5.5-9.4▲	7.5-10	28-34	40
Women %	0.2	0.4	0.8	1.5	3.0				

▲Jones Reported 24% within 2 years for AAA 5.0-5.9

*[83], **[88, 89]

1.5 Treatment for Abdominal Aortic Aneurysm

Surveillance of patients with small aneurysms

Aneurysms < 55 mm in men and < 50 mm in women are subject to surveillance and medical treatment aimed at secondary prevention. Based on the size of the aneurysm and the corresponding risk of rupture, surveillance is performed at certain intervals. The intervals and method of surveillance varies between different regions and countries and have recently been presented in a meta-analysis.[83] In England surveillance is conducted with ultrasound every 12th month in AAA's 30-44 mm's and every 3rd month in AAA's 45-54 mm. Revision of this surveillance algorithm has been argued by Dr Powell et al, suggesting less frequent exams for small aneurysms.[90]

The surveillance intervals in Stockholm, Sweden are slightly different (all based on ultrasound LELE): Every 24th month in AAA's 30-39 mm, every 12th month in AAA's 40-44 mm, every 6th month in AAA's 45-53 mm. AAA's >50 mm in women are evaluated for prophylactic surgery while men >53 mm are evaluated for surgery.

Prophylactic surgical treatment for an intact AAA

Patients with an CT-3D AAA diameter over 5.5 cm (5.0 cm in women) are generally evaluated for prophylactic surgery.[91, 92] Prophylactic surgery can be either open repair (OR) or endovascular aortic repair (EVAR). The latter method offers a shorter hospitalization with fewer major complications and lower short-term mortality. In Sweden 2012, 998

patients were treated with prophylactic surgery, 391 with OR and 607 with EVAR. The two methods have equal long-term mortality.[93, 94] EVAR requires life-long surveillance and is associated with a higher risk for re-intervention according to several studies.[93, 95-97] One large study has shown equal rate of re-intervention when incisional hernia-repair after OR is included.[98] Recent randomized trials have demonstrated very low 30-day mortality for low- to moderate risk patients treated with OR (1.3%) and EVAR (0.6%).[94, 95] Possibly the improved postoperative mortality is due to better medical treatment, improved per-operative care and centralized surgery, but a more careful selection of candidates offered prophylactic surgery might have affected the results.

The introduction of screening for AAA has increased the cohort of younger patients offered prophylactic surgery. Their lower age is a natural explanation to a lower postoperative mortality in geographical areas where screening is offered. The screening-detected patients are sometimes argued to be less afflicted by concurrent diseases.

Smoking cessation

Many (18-52%) patients with small AAA's are current smokers, according to screening-studies.[57, 66] A recent study has revealed that the impact of smoking on the risk for AAA is larger for women. [99] Continued smoking in AAA-patients is associated with a higher risk of cardiovascular event, higher risk of rupture and worse perioperative outcome.[87, 100] The recommendation is that AAA patients should be offered assistance to stop smoking.[101]

Medical treatment for AAA

The medical treatment for patients with AAA has three major aims; to decrease expansion rate and risk of rupture, and to limit cardiovascular events. There are several drugs currently under investigation for their effect on growth rate on small AAA. Several antibiotics have been tried with only a very small positive effect of roxithromycin in a meta-analysis from 2012.[102] [103]Best documented is the effect of medical treatment at the perioperative part of AAA treatment. The current European Society for Vascular Surgeons (ESVS) recommendation from 2011 is that statins should be started one month prior to elective repair and be continued for an indefinite duration. Regarding antiplatelet therapy the recommendation is "all patients with AAA should be started on aspirin therapy at the time of AAA diagnosis and this should be continued through the perioperative period as the risk of significant haemorrhage appears low".[35] The SVS (2009) recommends initiation of treatment with statin as well as ACE-inhibitors at diagnosis but in both cases state the recommendation to be weak and quality of evidence "low". Antiplatelet therapy is not mentioned in the SVS guidelines.[92] A recent (2014) Cochrane review found only one randomized trial regarding medical therapy in AAA-patients to review (this study regarded beta-blockers).

Statins

The positive perioperative effect of statins in AAA-patients in both elective and emergency repair is well documented. Evidence of decreased short- and long-term postoperative mortality, perioperative cardiac events and shorter hospital stay is present.[104-107] Prophylactic treatment with statins to patients under surveillance for small aneurysm is widely used but so far not backed-up by equally solid evidence. Several smaller retrospective cohort studies showed a decrease in growth rate[108-111] but two larger trials

failed to confirm this.[112, 113] Two meta-analyses have been published, one showing a small but significant decrease in growth rate with statin-use, one showing no difference.[87, 114] A recent (2014) large Danish trial has shown a reduced risk of rupture and a better postoperative outcome in AAA-patients treated with statins.[85]

Antiplatelet therapy

There are no randomized trials investigating the effect of antiplatelet use specifically in AAA-patients. There is evidence that long-term antiplatelet-therapy reduces risk of cardiovascular events by a 25%/year when used as secondary prevention in patients with a known vascular occlusive disease.[115] The ESVS recommendation is based largely on a meta-analysis including vascular patients, showing a benefit even as primary prevention in patients with no vascular occlusive disease. However, when the risk of serious bleeding was taken into account the net effect was so small that the review concluded that further studies are needed.[116] There is however evidence that patients with AAA have twice the risk of cardiovascular events compared to controls and the question can be raised in how many cases vascular occlusive disease is present but not diagnosed.[117]

The positive effect of antiplatelet therapy on AAA growth-rate is currently being explored with definite results in experimental models and promising results in humans.[118]

ACE-inhibitors

There is no consistent evidence supporting the use of ACE-inhibitors in AAA-patients.[119] One study showed a decrease in progression of disease,[120] while another showed the opposite.[121] There is an ongoing RCT comparing ACE-inhibitors to Calcium-channel-blockers and placebo.

Treatment for ruptured AAA (rAAA)

The mortality in rAAA is hard to estimate since a large proportion of patients do not reach hospital and die undiagnosed. According to registers from The Swedish National Board of Health and Welfare 849 patients died from ruptured aneurysms (thoracic and abdominal) in Sweden 2012. This is likely to be an underestimation since autopsies are seldom performed (12% in 2007).[60] Patients with an *untreated* rAAA have a mortality of 100%. In a large study made by Acosta et al 2006 the mortality from rAAA was estimated to 75% (included treated and untreated patients).[122]

The mortality from *treated* rAAA is easier to analyze. According to Swedvasc 2013 the 30-day mortality after OR for rAAA was 28%, after EVAR 21%. A recent meta-analysis over studies from 1999- the mortality ranged from 5-53% after EVAR and from 15-63% after OR.[123]

Regarding method of choice for rAAA current data suggests that the methods both have their advantages and disadvantages but overall have equal results.[123] EVAR-rate is increasing but not all centres have access to emergency-EVAR. In addition, not all aneurysms are suited to treatment with EVAR performed with standard-technique, creating a selection towards open surgery in AAA's with more complex anatomy. On the other hand, some centres perform open repair so infrequently that the technical skill to perform OR could potentially become endangered.

1.6 Population-based screening for AAA

Wilson and Jungner classic screening criteria[124]
1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination. 6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Screening for abdominal aortic aneurysms (AAA) has been evaluated in four large randomized trials, The Chichester Study[125], The Multicentre Aneurysm Screening Study (MASS)[126], The Western Australian Screening Study[49] and the Viborg trial.[127] Screening has been shown to result in a 40-50% decrease in aneurysm-related mortality.[39, 127-129] In the 13-year follow-up from the MASS-study screening for AAA was also associated with a 3% reduction in all-cause-mortality. The large screening trials included patients 10-18 years ago and reported a prevalence of 4-7.8% in men. Only the Chichester Study included women. Lately lower prevalence of 1.5-2.2% have been reported, indicating a change in the disease, possibly due to decreased smoking and improved preventive healthcare.[6, 44, 50] Cost-efficiency has been shown, even with decreasing prevalence of disease taken into account.[130, 131] As a result, population-based screening programs for men have been implemented in England (2009), Scotland (2012), Wales (2012), Sweden (2006), Oslo in Norway (2011), Northern Ireland (2012) and in the US as part of Medicare.[132] In Italy and New Zeeland screening trials are ongoing and in Finland and Denmark the cost-effectiveness of screening has been positively evaluated but screening has not been implemented.

Screening recommendations
Guidelines regarding selection of groups for screening have been published 2005-2012 by several organizations such as US Preventive Services Task Force (USPSTF)[133], American College of Cardiology (ACC/AHA)[134], National Screening Committee (NSC United Kingdom)[135], Society of Vascular Surgery (SVS)[92], Canadian Society of Vascular Surgery (CSVS)[136], and ESVS.[35]
The guidelines are fairly consistent regarding the recommendation to perform one-time screening in ever-smoking men 65(-75) years old, but vary regarding non-smokers, women and first-degree relatives to patients with AAA. Regarding women, USPSTF and ACA/AHA recommends against screening in women regardless of family history and smoking whilst SVS and CSVS recommends screening in women >65 with one (SVS) or more (NSVS) risk factors (i.e. smoking, first degree relative). In The British guidelines by

NSC one-time screening of 65 year old men is recommended, but no recommendation regarding women is made. The ESVS recommends screening of first-degree relatives above age 50. The recommendation by USPSTF against screening of women is based on lack of benefit in long term mortality and rupture rate after 10 years in the Chichester study[52] where the frequency of aneurysms among women were 1.7%.

The AAA-screening program in Stockholm.
Stockholm County Council started a population based screening program in August 2010, by inviting all 65-year old men to a once in a life time screening with ultrasound. All men turning 65 since July 1st 2010 residing within the Stockholm county are invited to the AAA screening program as part of the Stockholm County Council screening program. The coordination of the screening program is centralized to the Stockholm-Gotland Regional Cancer Center. The monitoring of screening, including issuing of invitations, reminders, measuring-results (i.e., the diameter of the aorta), are registered in a web-based program. The invitation letters are written in Swedish, are sent by regular mail and include brief information about the disease and a pre-scheduled appointment for ultrasound examination at one of two screening centers, both located in the city-center. There is a possibility of rescheduling, online or by telephone. Persons who do not participate without notifying the screening organization receive one reminder with another prescheduled appointment. Up until January 2012 the ultrasound-examination had a fee of 140 SEK (approx. 12€), after this date it became free of charge. At the ultrasound screening center the aortic diameter is measured with ultrasound using Leading Edge to Leading Edge-technique (LELE), an anteroposterior longitudinal measurement including the near, but not the far, aortic wall. All men with a maximum infrarenal aortic diameter ≥ 30 mm are given brief written information about the disease together with an appointment at the vascular clinic within 2 weeks. All men with an infrarenal diameter < 30 mm are declared free from AAA and receive that information at the ultrasound screening-center.[37]

Participants and non-participants in screening programs
The Swedish participation rates in screening programs for others diseases; breast cancer (75-85%)[137] colorectal cancer (39%)[138] and cervical cancer (55%)[139] , are high compared to the rest of the world. Both in Sweden and internationally, the participation rates are reported influenced by socioeconomic factors such as marital status, income and level of education, but also by immigrant status and travel distance to examination center.[138-140] It has been shown, both in the area of colorectal cancer screening[141, 142] and that of AAA[143], that non-participants in screening to a greater extent have an unhealthy lifestyle and to a greater extent are smokers. It is possible that the non-participants of AAA-screening are at greater risk of AAA, which motivated us to find modifiable factors that could be used to increase the participation rate. A questionnaire study published 2013 showed that 40% of non-participants were willing to reconsider their decision after having received additional information.[144] It also showed that many refrained from participation for practical reasons.

2. Aims with this thesis

Study I

The primary aim was to assess the prevalence of AAA among siblings to persons with AAA and to compare characteristics of siblings with and without AAA.

The secondary aim was to investigate the proportion of siblings already diagnosed by opportunistic screening.

Study II

The primary aim with this study was to investigate if siblings to AAA-patients in the North part of Sweden (Norrbotten) have a higher prevalence of AAA compared to siblings to AAA-patients in the Stockholm region (Mid).

The secondary aim was to identify relevant ages to screen for AAA in male and female siblings.

Study III

The primary aim was to identify the most prominent individual socioeconomic and medical factors influencing participation rates in the population based screening program.

The secondary aim was to investigate the health-status of the non-participants in order to view their risk of disease.

Study IV

The primary aim was to compare postoperative outcome within 30 days in patients with screening-detected AAA vs non screening-detected AAA in a population-based setting. Secondary aims were to analyze mortality up to one year, preoperative comorbidity and choice of surgical method. Our hypothesis was that patients with screening-detected AAA have a better postoperative outcome due to less preoperative comorbidity.

3. Patients and Methods

3.1 Study designs

Table VI. Study designs

Study	Design	Participants	Method	Comparison	Primary outcome
Study I	Cross-sectional Cohort/ Prevalence study	Probands=412 Siblings=150	Interview+ ultrasound	Siblings with AAA vs those without	Prevalence AAA siblings <80 in Stockholm
Study II	Cross-sectional Cohort/ Prevalence study	Probands=483 Siblings=379	Interview+ ultrasound	Study I siblings Stockholm	1. Prevalence AAA siblings North comp to Mid 2. Ages at detections of AAA in siblings
Study III	Retrospective Longitudinal Cohort study	24 139	Crosslinked registry data-extraction	Participants vs non-participants in screening	Reasons for non-participation in screening
Study IV	Prospective Longitudinal Cohort-study	700	Registry data-extraction Swedvasc	Screening-detected vs non screening-detected	Complications after surgery

Table VII. Naturally none of the studies included in this thesis could have been conducted without major support and contributions of my mentors and co-authors. Table VII clarifies the extent of my participation in each project.

	Study I	Study II	Study III	Study IV
Idea	No	No	Yes	No
Study-design	Yes	Yes	Yes	Yes
Ethical permit-application	Yes	Yes	Yes	No
Data collection	Yes (all ultrasounds but not interviews)	No	Yes (extraction from registers)	Yes
Data organisation	Yes	Yes	Yes	Yes
Data analysis	Yes	Yes	Yes	Yes
Statistics	Yes	Yes	Yes	Yes
Manuscript writing	Yes	Yes	Yes	Yes
Submission +revision	Yes	Yes	Yes	Submission No, revision Yes

3.2 Hospital settings in Stockholm County

The Stockholm County is a geographical area covering the City of Stockholm and surrounding area. There are almost 2.100.000 inhabitants living in 6500 km^2 including 6000 people living on 150 islands without road access. The region has two Centers for Vascular Surgery, the Karolinska University Hospital and Södersjukhuset, both located near the city center. No major vascular surgery is performed outside these centers. Almost all patients with an AAA get referred to a vascular specialist in one of these clinics. Those not considered eligible/having benefit from prophylactic surgery are referred back to general practitioners. Those considered possibly eligible are considered for surgery surgery or enrolled in a surveillance program.

3.3 Registries used in this thesis

Registries from the National Board of Health and Welfare (NBHW)[60]
All Swedish citizens have a personal identification number consisting of year and date of birth, followed by a four-digit number.

All in-hospital admissions and out-patients visits are registered and collected by the *National Board of Health and Welfare* (NBHW). This central registry covers all in-patient health care obtained within the borders of Sweden, which is registered on an individual level (hospital stay, diagnoses, operations and causes of death). All surgical procedures are recorded as well as all diagnoses and, if applicable, causes of death.

All *outpatient visits* to medical specialist centers such as a vascular clinic are registered in the same fashion (visits to general practitioners are not listed). All deaths are registered with one or more causes of death.

The majority of causes of death outside hospitals are decided by primary-care physicians and made on the basis of known pre-existing medical conditions. Autopsies were performed in 12% of all deaths in Sweden (2007).[145]

The validity of the NBHW-registry is very high regarding in-hospital care. All hospital reimbursements are based on the registered diagnoses and this keeps the hospitals and doctors motivated to report.

The registry present some general data open-access online but all data on an individual level is kept under rigorous control. Individual data can only be extracted at a cost and in a coded format and application for data extraction is a thorough process.
Data extraction was performed for study II and III.

Public Health Agency of Sweden[77]
Data regarding population, ages, family size, marital status, economics, education and immigration-status are available in Swedish databases at the Public Health Agency of Sweden. They also present data regarding life-styles (i.e. smoking, alcohol consumption) and preventive health measures. In the same fashion as described above, the registry present some general data open-access online but person-specific data are kept under rigorous control. Individual data can only be extracted in a coded format and application for data extraction is a thorough process. Data extraction was performed for study II and III.

Swedish National Registry for Vascular Surgery "Swedvasc"
Sweden's National Registry for Vascular Procedures, Swedvasc, covers all centers performing AAA-surgery in the country. The Registry is web-based and data are registered prospectively. Surgeons register perioperative data and complications at 30 days. Data on perioperative medication are not available. Every month the Registry is interconnected with the Swedish Death Registry, thereby allowing for accurate data regarding mortality in all the registered patients. The Registry does not include causes of death. The Registry has been found to have a 93.1% external validity for registration of abdominal aortic aneurysms (AAAs).[146, 147] All hospitals performing elective repairs contribute to Swedvasc but a few ruptures may be operated in hospitals not doing elective repairs and some centers do not reach 100% registration-rate each year.

In July 2010, a new mandatory variable requiring information concerning whether the aneurysm was detected by screening or not was implemented. We utilized this registry in study and IV. Since this screening variable has not been validated previously, a random sample of 100 patients was cross-matched for the variable against medical record data from four of the population-based screening centers.

3.4 Patients and Methods studies I and II

In these two studies we investigated the prevalence of AAA among siblings (aged ≤ 80) to AAA-patients with the aim of describing prevalence, the siblings' ages at detection and regional differences in sibling-prevalence. A total of 529 siblings were included and examined in the two studies.

The Regions
The Mid region in studies I and II cover AAA-patients/siblings living in Stockholm County. The Stockholm area covers a population of almost 2.1 million inhabitants living in 6 500km^2.
The North region study II covers AAA-patients/siblings living in the county of Norrbotten which has 249.000 inhabitants spread over 26 671 km^2.

Probands and siblings in Mid region, Stockholm
All living patients treated or monitored for AAA in Stockholm Jan 2008 through Dec 2010 were invited to join the study (n=322). To avoid identifying aneurysms in patients whom we later would be unlikely to offer prophylactic treatment, siblings older than 80 years were not included. AAA-patients were contacted through letter or at their hospital visit; 779 siblings were identified of which were 449 alive. Permission to contact siblings was obtained from the proband patients. All siblings <80 years living in the Stockholm county were considered eligible and were invited to participate in the study (n=174). 42 siblings were not invited due to proband inability to find/give contact information, 14% (n=24) declined participation or were ineligible for medical reasons. 10 participating siblings had recent (<6 months) normal scans of the aorta, and gave consent to access medical charts. Deceased siblings were not included or analyzed regardless their cause of death. In the cohort of 778 reported siblings 289 were deceased (37%). Cause of death was not registered.

Probands and siblings in North region

All consecutive living patients treated or monitored for AAA at Sunderbyns Hospital January 2008 through August 2012 were identified in the medical charts. 338 patients were invited to join the study. Eligibility-criteria were the same as in Stockholm.

This generated 447 living, preliminary eligible siblings who were invited to participate in a structured interview followed by a subsequent ultrasound exam of the aorta.

Of the 447, 10% (n=46) declined participation, 9 could not be reached and 13 were ineligible for medical reasons. Of the 46 who declined participation 10 volunteered the information that they had already passed an ultrasound exam with a normal result. 379 siblings gave informed consent and participated in the study. Of 16 siblings with a known AAA before the study 11 gave permission to view their medical charts. In the North cohort of 1470 reported siblings 479 siblings (33%) were deceased.

Interview

A research nurse conducted a structured telephone-interview with all consenting siblings regarding basic social and health related issues, prior to booking an ultrasound appointment. All medical and social history was self-reported from the siblings.

Definitions

"Age at detection" for the siblings with AAA was defined as the person's age at the first reported diagnosis, either found in hospital charts, or from date of the ultrasound scan. Current daily smokers and sporadic smokers were considered "current smokers" and previous smokers with >4 weeks abstinence were considered "ex smokers". Daily, previous and sporadic users of snuff were considered "ever snuff users". "Heart disease" was defined as previous ischemic cardiac event, diagnosed pectoral angina or diagnosed congestive heart failure.

Ultrasound

In the two regions, 499 siblings were examined with abdominal ultrasound and for 30 siblings information was extracted from medical charts/x-ray charts.

In Stockholm (Mid) one investigator (Linné) performed all ultrasounds at one location using a logiqE ultrasound machine from General electrics. In Norrbotten (North) one investigator (Forsberg) performed all ultrasounds at two locations; Gällivare and Sunderbyns hospital. The investigators were both validated for aortic measurement-technique at a central core lab in Stockholm prior to the study start. Ultrasound was performed with curved array transducer and a Logiq S8 from General Electrics (GE)© in North. The aortic diameter was measured using both Outer-to-Outer technique (OTO) and Leading-Edge to Leading-Edge technique (LELE) with an infrarenal, max pulsewave, AP-diameter ≥ 30 mm in men and ≥ 27 mm in women were considered AAA.[2, 35, 43] When presenting frequency of aneurysm OTO-measures were used.

Statistics

Univariable logistic regression models were estimated for aneurysm as outcome where the variables with a p-value < 0.1 were included in a multivariable model. The variable age was dichotomized in the main model but was also included as a continuous variable and modeled using a restricted cubic spline with 4 degrees of freedom to visualize the functional

form. The Hosmer-Lemeshow godness-of-fit was performed for the multivariable model and outliers were checked by means of the dfbetas whereas the variance inflation factor (VIF) was used to detect possible multicollinearity. Interactions were tested for within the multivariable model and interactions were also used to visually display the combination of characteristics in a Forest plot. Data were analyzed in SPSS 18.0. P values below .05 were considered significant.

Registers and regional differences
Data from for this study were extracted from the National Board of Health and Welfare for the counties Stockholm and Norrbotten, concerning all inhabitants from age 40 and up. The data were reported as average yearly number of patients treated/100 000 inhabitants. Regarding medication, data were collected from the Pharmacy-Registry provided by The Swedish National Board of Health and welfare. This register is based on prescriptions and registers all filled prescriptions on an individual level. Number of retrieved daily doses of lipid-lowering (HMG-COA reductase inhibitors (i.e. Statins) medication, the most commonly used in Sweden, was collected from this registry. The data were presented as number of daily doses/100 000 inhabitants.
Smoking data were collected from The Public Health Agency of Sweden.[77] Smoking data in this register is derived from large health surveys in which data is self-reported by inhabitants aged 15-84. Smoking data were collected for the Regions of Stockholm and Norrbotten.

3.5 Patients and Methods study III

In this we study compared socioeconomic factors between participants and non-participants in AAA-screening with the aim of finding reasons for non-participation.

Study population.
The study population (fig III not in article) consisted of all invited men within the Stockholm screening program from its start July 2010-July 2012 (n=24139) divided into participants (n=18876) and non-participants (n=5443). Data were collected regarding all men invited to screening from the central screening organization at the Regional Cancer Center and matched with databases from Statistics Sweden and National board of Health and Welfare. The loss of matching was 0%. From these registries data was collected regarding marital status, income, home-address, immigration, education, health-care visits, diagnoses, death and causes of death. All health care visits and diagnoses were collected from the date of the invitation and 10 years back in time.

Definitions
Income was registered for the age of 60 to avoid misclassification due to retirement. All men born outside Sweden were considered immigrants and all men born in Sweden were considered Swedish. Race is not registered in Swedish health care charts. All Swedish-born men re-immigrating to Sweden after living abroad were assessed as Swedish. County based smoking data were obtained from The Public Health Agency of Sweden describing percentage of daily smokers of men aged 15-84.[77]

Statistics

Non-participants deceased within 4 weeks from the invitation were excluded from the analysis (n=1). Statistical analysis was performed using SPPS software 21 (IBM Corporation, Armonk, NY). For the socioeconomic factors, univariable logistic regression was used to establish OR Crude. OR adjusted was obtained using multivariable logistic regression, adjusting for all variables stated in table II. Income was divided into quintiles based on number of persons, as were travel-distance. From the group of immigrants in "Immigration year" re-immigrating Swedes have been excluded from the analysis (n=975). The comparison regarding co-existing diagnoses and health-care use was done using Chi-2-test, $P<0.05$ considered significant. All hospital admissions, outpatient visits and diagnoses dated after the invitation to screening were excluded from the analysis.
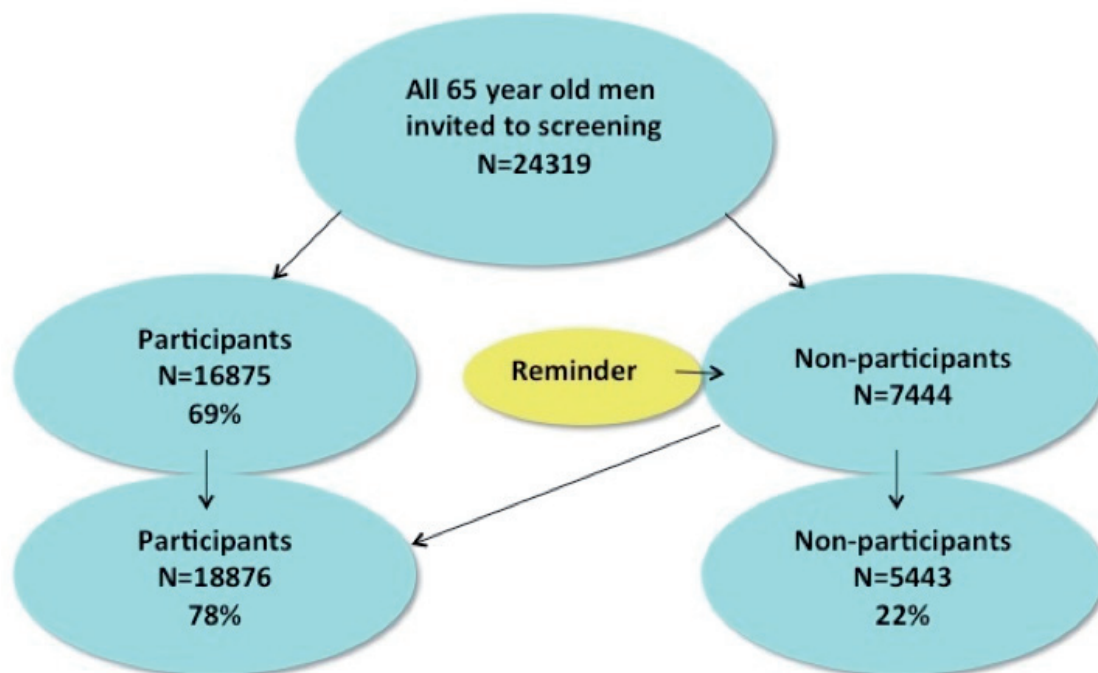
Fig III. Participants and non participants in screening (not in manuscript)

3.6 Patients and Methods study IV

Study IV aimed at comparing postoperative outcome in patients with screening-detected AAA vs non screening-detected AAA in a nationwide material (Swedvasc).
Also, to compare preoperative comorbidity and choice of surgical method in the two groups.

Study population

Data were extracted from the Swedish National Registry for Vascular Surgery (Swedvasc). Eligibility criteria were all elective aortic repairs from May 7th, 2010, to January 15th, 2013 (n=2135). All women were excluded (n=164). To exclude procedures performed on any other indication than AAA size (iliac aneurysms, aortoiliac occlusive disease), all repairs in patients with an aortic diameter of <50 mm were excluded (n=164). A few centers

screen for AAA while the patient is being examined for other vascular diseases, with the result that some AAA´s are classified as *screening-detected* without being identified by *population-based screening*. In order to minimize this bias, data were collected from all centers regarding age groups offered population-based screening and these data were matched with Swedvasc-data on the year of birth of the patient. Patients who could not have been subject to population-based screening were redirected to the non-screening detected group. Patients whose screening status was "unknown" were excluded (n=12). When randomly selecting the 350 age-matched controls, age matching had to allow for a span of 2 years in order to achieve a sufficient number of controls. The screening-detected aneurysms (n=350) were then compared with those of age-matched controls with non-screening-detected aneurysms (n=350) regarding comorbidity, choice of surgical method, mortality, and complications after surgery. For each screening-detected AAA, an age-matched control (within 2 years) was selected in the non-screening-detected cohort. Primary endpoint was a combined endpoint of mortality and major complications within 30 days. Secondary endpoints were differences in postoperative mortality (30 days, 90 days and one year), preoperative comorbidity and choice of surgical method. A combined endpoint for major adverse events, including death, AMI, stroke, amputation, bowel ischemia and renal failure, was constructed in accordance with the ACE trial.[94] Comorbidities reported in Swedvasc were defined as follows; Diabetes: diabetes with medical treatment, Cardiac disease: history of coronary artery disease or congestive heart failure. Hypertension: hypertension with medical treatment, Pulmonary disease: COPD or emphysema or other chronic pulmonary disease with symptoms. Preoperative renal failure was defined as a creatinine-level above 150 in accordance with a previous Swedvasc-study.[148] Ever smoking was defined as current or previous smoking. Age was categorized in two groups to create two groups of similar size; <68 years (n=346) or ≥ 68 years (n=354). Limited power did not allow for more subgroups of age.

Statistics

Randomization and all statistical analyses were performed using IBM SPSS Statistics 22.0. For two-group comparisons Fisher's and Mann-Whitney tests were used, as appropriate. Any P-value of less than 0.05 was considered significant and all tests were two-sided. Cases with missing data were excluded from corresponding analysis as noted in tables and figures.

Binary logistic regression was used for the analysis of risk factors possibly influencing the major adverse events at 30 days and mortality within 90 days. A univariable analysis was performed followed by multivariable adjusted analyses. Variables introduced "a priori" to the adjusted models were screening status, age and surgical method (OR or EVAR). The limited number of events did not allow for further adjustments.

4. Results

4.1 Overall results

The most important results from the four studies included in this thesis are:

Study I and II. Male and female siblings to AAA patients have a very high prevalence of AAA (all 10%, sisters 6%, brothers 16%). The youngest male was 50 and the youngest female 58. We found 53 siblings with AAA. Of all found siblings with AAA 16 had a large AAA (>5cm or operated). Among the siblings with large AAA, 8 (50%) were less than 65 years old.
We could not demonstrate a regional difference between North and Mid Sweden.

Study III. The frequency of AAA in 65-year old men in Stockholm is 1.4%. Participation in screening for AAA in men is high in Stockholm (78%) but varies between 55-86% in different subgroups. These variations depend on socioeconomic status, immigration status and travel distance to examination center. Non-participants in screening have more Chronic Obstructive Pulmonary Disease and cardiovascular disease and are hospitalized to a greater extent and are probably at higher risk of having AAA.

Study IV. Screening-detected men with AAA have the same prevalence of comorbidities as non screening-detected men of the same age. Open repair is used more often i screening-detected compared to non screening-detected. Screening-detected men have a good outcome after aortic surgery with a 30-day mortality of 0.6%, 90-day mortality of 1.1% and a 1-year mortality of 2.9%. The outcome for screening- detected men was better in terms of 90-day mortality compared to controls.

4.2 Results study I and II

From the two regions 529 siblings, age range 45-80, were enrolled in these studies, 253 (48%) were brothers and 276 (52%) were sisters. Demographics from all siblings are presented in table VIII (not in manuscript).

Stockholm (Mid)

150 siblings were included from Mid. There were 66 brothers and 84 sisters participating from 98 families. Mean age was 66.3 years SD 7.1.

16 (11%) of the 150 included siblings had previously recently been screened for AAA or had a known AAA (n=6). The remaining 134 were examined with ultrasound.

Demographics of the Stockholm-siblings: 59 % were current or previous smokers (ever-smokers). Among the Stockholm siblings, 11% (n=16) were found to have an AAA, 17% (n=11) of brothers and 6% (n=5) of sisters. Six of the siblings had a previously diagnosed AAA of which 5 had been treated surgically. Mean age in the AAA-diagnosed siblings was 71.6 vs 65.7 in the non-AAA group. Among siblings with AAA 81% were ever-smokers compared to 59% of the non-AAA siblings. Out of the 16 AAAs 6 were >50mm, 1 was 40-49, 6 were 30-39mm, 3 was 27-29mm (females). In the univariate regression analysis male sex vs female was associated with an increased risk to have an AAA, as did age >65. These three variables were introduced in a multivariable model. Factors associated with increased risk of AAA in multivariate analysis were male sex, and age >65y. Smoking did not contribute with an increased risk.

Table VIII. Demographics and risk factors of siblings in North and Mid with and without AAA. (not in manuscript).

	AAA siblings n=53 n (%)	Non-AAA siblings n=476 (n) %
Mean age (SD)	71.2 (5.8)	66.7 (7.1)
Never smoker	5 (10)	174 (37)
Ex smoker	29 (56)	216 (45)
Current smoker	16 (31)	86 (18)
Hypertension	29 (57)	238 (50)
Heart disease (IHD/CHF)	16 (31)	100 (21)
COPD/Asthma	4 (8)	59 (12)
Diabetes	6 (12)	47 (10)
Statins	23 (45)	147 (31)
ASA	29 (58)	122 (26)

Three patients excluded from presentation of risk factors/medications due to missing data. Four patients excluded from presentation of Heart disease due to missing data.

Norrbotten (North)

379 siblings were included from North. The mean age was 67.5 SD 7.1. Demographics for the screened siblings in North and Mid are presented in table VIII. There were 192 sisters

and 187 brothers participating from 169 families (number of participating siblings from each family ranging from 1-11. Of the 379 siblings, 8 had undergone aortic repair and 8 had a known AAA under surveillance.

The prevalence of AAA in siblings in North was 37/379 (10%), brothers 26/187 (14%), sisters 11/192 (6%) (table IX). Of the 37 identified cases with AAA 21 were new cases and 16 were cases already known. Of the 37 siblings with AAA 2 were never-smokers.

Risk factors and AAA prevalence in siblings North compared to Mid

There was no difference in the prevalence of AAA in siblings aged 40-80, residing in the North compared to Mid-region (p=0.75) (table IX).

There was no difference in age or occurrence of smoking, heart disease, chronic obstructive pulmonary disease (COPD), diabetes, hypertension or use of ASA between the siblings in North and Mid (table X). Siblings in North more frequently reported that they medicated with statins (p= 0.040) (table X).

Table IX. Frequency of AAA in Sweden: Siblings in Mid and North

	AAA Siblings Mid* (n=150) n (%)	CI for proportions	AAA Siblings North (n=379) n (%)	CI for proportions	p*
Male	11 (16.7)	(7%-26%)	26 (13.9)	(9%-19%)	0.61
Female	5 (6.0)	(1%-11%)	11 (5.7)	(2%-9%)	0.94
All Sibl	16 (10.6)	(7%-13%)	37 (9.8)	(6%-16%)	0.75

*Chi^2-test

Table X. Risk factors in Siblings in Mid Sweden (Stockholm)[16] compared to North (Norrbotten).

	Siblings Mid* (n=150) n (%)	Siblings North (n=379) n (%)	p
Median Age (IQR)	66 (62-71)	68 (63-73)	0.04
Smoking			0.41
Never smoker	58 (38.7)	121 (32.0)	
Ex smoker**	63 (42.0)	182 (48.1)	
Current smoker	29 (19.3)	73 (19.3)	
Heart disease*	32 (21.3)	84 (22.3)	0.91
Hypertension	79 (53.0)	188 (50.4)	0.63
COPD	11 (7.5)	52 (13.8)	0.052
Diabetes	16 (10.7)	37 (9.8)	0.75
ASA	39 (26.0)	112 (29.8)	0.46
Statins	37 (24.7)	134 (36.7)	0.008

*Previously published data[16]
**Ex smoker: Stopped smoking >4 weeks ago
***Heart disease: Previous ischemic cardiac event, angina or congestive heart failure.
COPD: Chronic Obstructive Pulmonary disease
Comparison of median age tested with Mann-Whitney. Other comparisons Fishers exact test.

Age of siblings detected with AAA

In the entire cohort of 529 siblings from Mid (Stockholm) and North (Norrbotten) there were 53 siblings with AAA, 16 sisters and 37 brothers. Information about age at detection was available for 45 patients. There was one brother who underwent prophylactic surgery at the age of 50. No other siblings were < 55 years at the time of detection of an AAA. In all ages, 16/45 (36%) siblings had an AAA that was larger than 5cm or had been treated surgically. Among the 16 siblings who had large aneurysms 8 (50%) where younger than 65 (table XI).

Table XI. Age at detection of AAA in 529 siblings from North and Mid Sweden

	Sisters n=276	Brothers n=253	All siblings n (%)	Siblings with AAA > 5 cm or performed surgery**, n
<55	0 /20	1/15	1/35 (3)	1*
56-60	2/29	4/31	6/60 (10)	3
61-65	2/64	7/48	9/112 (8)	4
66-70	4/65	12/75	16/140 (11)	4
>70	8/98	13/84	21/182 (12)	4
Sum	16/276	37/253	53/529 (10)	16

* Elective AAA-surgery at age 50.
**Data regarding size missing in 8 patients

4.3 Results study III

Study population and frequency of AAA

The participation-rate increased after reminding letters from 69.4% to 77.6% for the invited 65-year old men (n=24319) (fig III). The majority, 80% (n=19479) of invited men were Swedish, 20% (n=4851) were immigrants. The participation rate among Swedes was higher than among immigrants (80 vs 68%).

The prevalence of AAA detected in screening was 1.4% (n=265). In addition, from the Swedish National Registry of Health, another 97 previously diagnosed AAA-patients, under surveillance and with previous aortic repairs, were identified. The prevalence among all invited men, including screening-detected and previously known, was 1.5% in 65 years old men.

The prevalence of AAA varied with socioeconomic factors as described in table XII. Swedes, immigrants from Europe, and non-European immigrants had similar prevalence rates (1.7%, 1.4%, and 0.8%).

Risk factors for non-participation

All factors analyzed were associated with participation rate in screening in crude analyses (table XIII). The crude odds ratios (OR crude), and adjusted odds ratios (OR adjust) for

not participating in screening are listed in table XIII.

The strongest risk factors associated with not participating in screening were low income (Adjusted OR 2.76 95% CI 2.45-3.10), immigration within the last 5 years (Adjusted OR 3.25 95% CI 1.94-5.47) and marital status single/divorced (Adjusted OR 2.23; 95% CI 2.08-2.39).

The travel distance varied from 0-118 km with a mean of 22 km. There was an increased risk of non-participation in the group with a travel distance longer than 31 km (Adjusted OR 1.23 95% CI 1.11-1.37).

Table XII: Descriptives of study population and frequency of AAA for different socioeconomic groups, data collected on an individual level.

Descriptives and frequency of AAA	% of all invited (n=24319)	% AAA detected in screening* (n=265)	% AAA* Known before screening (all invited men)** (n=97)
All	100	1.4	0.4
Swedish-born	80	1.4	0.3
Immigrants Europe	13	1.7	0.6
Immigrants rest of World	7	0.8	0.5
Marital status Married	60	1.2	0.4
Single/divorced	37	1.5	0.4
Widower	3	0.6	0.0
Travel distance 0-5 km	20	1.5	0.3
6-14 km	20	1.2	0.5
15-22 km	19	1.5	0.4
23-31 km	22	1.2	0.5
31-118 km	19	1.1	0.4
Education high (university)	21	0.9	0.3
middle (upper middle school)	35	1.4	0.4
low (9 year compulsory school)	41	1.8	0.5
Income 1st quintile (highest)	20	1.0	0.2
2nd quintile	20	0.9	0.2
3rd quintile	20	1.5	0.5
4th quintile	20	1.7	0.6
5th quintile (lowest)	20	1.5	0.6

*Frequency calculated in percentage of participants in screening (n=18876). 18 AAA-patients excluded from socioeconomic analysis due to missing data.

** Frequency calculated by percentage of all invited men

Health care use and comorbidity

Analysis of health care use revealed that 29.1% of the men participating in screening had >2 in-hospital admissions within the past 10 years before invitation to screening, compared to 32.9% in the non-participant group (p <0.0001) (table XIII). Regarding out-patient visits in the past 10 years before invitation to screening 76.3% of the non-participants had >2 such visits compared to 85.1% among the participants (p < 0.0001). The non-participants had a significantly higher frequency of Chronic Obstructive Pulmonary Disease (COPD), Stroke, Diabetes, renal failure and Thoracic Aortic Aneurysms. The frequency of malignancy was higher in the group of participants, while there was no significant difference in the

frequency of ischemic heart disease between the groups (table XIV).

When describing comorbidity in screening detected (n=247) vs previously known (n=97) AAA-patients (not in table), there was no significant difference regarding the frequency of Ischemic heart disease, Stroke, diabetes, Chronic Obstructive Pulmonary Disease or malignancy. There was a difference in the frequency of renal failure (12% v 0.4% p<0.0019) between the AAA-patients detected prior to screening and the screening detected AAA-

Table XIII: Participation rate in screening and risk (OR) of non-participation in screening according to different socioeconomic variables.
Univariable logistic regression (OR crude) and multivariable logistic regression (OR adjusted.)

Risk of non-participation in screening	N	PR %	OR crude	95% CI	OR Adjusted	95% CI	p
Disposable income (missing 329)							
1st quintile (highest)	4797	86.5	1.00				<0.001*
2nd quintile	4794	86.2	1.02	0.91-1.15	0.93	0.82-1.06	0.283
3rd quintile	4795	82.4	1.38	1.22-1.53	1.15	1.02-1.30	0.024
4th quintile	4798	74.5	2.19	1.97-2.43	1.66	1.48-1.88	<0.001
5th quintile	4806	60.9	4.10	3.71-4.55	2.76	2.46-3.10	<0.001
Marital Status (missing 302)							
Married	14491	84.6	1.00		1.00		<0.001*
Single/divorced	8889	68.4	2.52	2.38-2.68	2.23	2.08-2.39	<0.001
Widower	637	77.6	1.56	1.29-1.89	1.66	1.35-2.04	<0.001
Travel distance (missing 1124)							
0-5 km	4634	78.7	1.00		1.00		<0.001*
6-14 km	4604	77.4	1.08	0.98-1.19	0.99	0.89-1.10	0.880
15-22 km	4333	77.6	1.07	0.97-1.18	0.97	0.87-1.08	0.566
23-31 km	5122	79.9	0.93	0.84-1.02	0.97	0.87-1.08	0.527
31-118 km	4502	75.7	1.19	1.08-1.31	1.23	1.10-1.37	<0.001
Immigration							
Native Swedish	19637	80.0	1.00		1.00		<0.001*
Immigrant since >20 years	3735	70.9	1.63	1.51-1.76	1.31	1.31-1.20	<0.001
Immigrant since 5-19 years	636	66.6	2.02	1.71-2.93	1.48	1.22-1.78	<0.001
Immigrant since <5 years	311	51.6	3.71	2.96-4.65	3.25	1.94-5.47	<0.001
Education (missing 537)							
University	8564	81.7	1.0		1.0		<0.001*
Upper secondary school	10032	79.4	1.16	1.08-1.25	0.95	0.88-1.04	0.29
Elementary school 9 years or less	5186	70.6	1.87	1.72-2.02	1.28	1.16-1.40	<0.001

*= p-value for trend

Table XIV: Comorbidity and use of health care in participants compared to non-participants

	Participants N=18876	Non-participants N=5443	p
Health Care use 0-10 years prior to invitation to screening	**N (%)**	**N (%)**	
> 2 in-hospital-care occasions	5492 (29.1)	1790 (32.9)	<0.001
> 2 outpatient visits	16063 (85.1)	4153 (76.3)	<0.001
Comorbidity	**N (%)**	**N (%)**	**P**
IHD	1397 (7.4)	403 (7.4)	0.100
COPD	239 (1.3)	156 (2.9)	<0.001
Diabetes	1519 (8.0)	527 (9.7)	<0.001
Stroke	530 (2.8)	245 (4.5)	<0.001
Renal failure	216 (1.1)	87 (1.6)	0.009
Malignancy	2076 (11.0)	471 (8.7)	<0.001

IHD= ischemic Heart Disease, COPD= Chronic Obstructive Pulmonary Disease
All diagnoses collected prior to invitation to screening.

patients.

Participation and smoking. Smoking prevalence data for men on a group level (15-84 year old men) were available for 11/25 municipalities. 14 municipalities had, according to FHI, statistically unreliable data due to small numbers and were therefore not available. However, the 11 municipalities with reliable data constituted 74 % (n=17990) of the invited men in our cohort. The relation between high percentages of daily smokers and
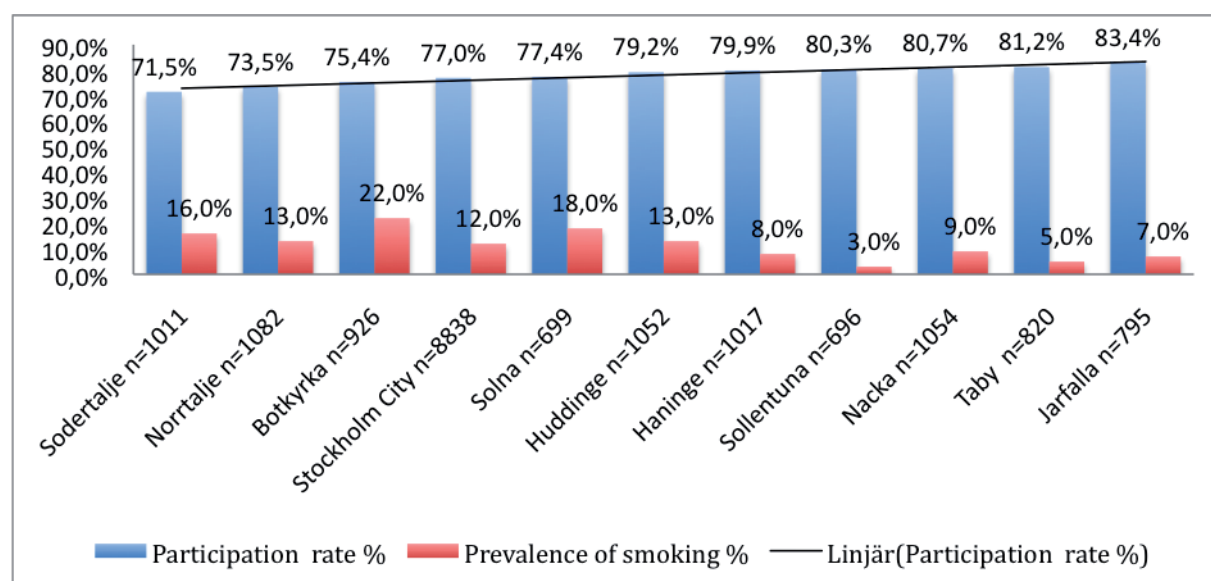

Fig IV: *Participation rate in screening and percentage of daily smokers in 16-84 y old men, by regional area.*
N=17990. 14 municipalities had unreliable smoking data due to small numbers and have been omitted.

low participation-rates are shown in fig IV.

4.4 Results study IV

Baseline Data, Comorbidity, and Choice of Surgical Method
There were no differences in baseline characteristics or comorbidities besides age, which was lower in the screening-detected group than in the non-screening-detected group (median 66 (IQR, 65-70) vs. 68 (IQR, 66-72), P <0.001 (mean age 68.0±3.5 vs. 69.1±4.1)) (Table XV). The necessary allowed age span when randomly selecting controls (see Methods) explains the age-difference between the groups. As shown in Fig V, open repair (OR) was more usual among patients with screening-detected aneurysms than among those with non-screening-detected aneurysms (56% vs 45%, P=0.005). Figure VI (not in manuscript) show change in choice of therapy over time (2010-2012).

Complications After Surgery
Overall, both groups had few postoperative complications at 30 days, but there were more complications after open surgery than after EVAR (table XVI). There was no difference in complication rates between patients with screening-detected and those with non-screening-detected aneurysms when separated into OR and EVAR (Table XVI). The frequency of major adverse events (combined endpoint: death, AMI, stroke, amputation, bowel ischemia, renal failure) was equal in screening-detected vs. non-screening-detected cases after OR (6.2% vs. 10.2% P=0.23) and after EVAR (1.9% vs. 3.6%, P=0.52)(Table XVI). Multivariable logistic regression (Table XVII) shows no difference in risk of major adverse events for non screening-detected patients (OR 1.64, 95% CI 0.82-3.25) when adjusted for age and method of intervention (EVAR or OR). The infrequent outcome (major adverse events at 30 days) did not allow further adjustment for potential confounders.

Mortality After Surgery
Mortality at 30 days, 90 days, and 1 year is presented for all patients and separately for OR vs. EVAR (table XVIII). At 30 days and 1 year, and in both types of aneurysm repair, there was no difference in mortality between the groups. Mortality at 90 days in screening-detected patients treated with EVAR was lower than in patients with non-screening-detected AAAs (0% vs. 3.1%, P=0.04, Table XVII). The 90-day mortality after OR did not differ between screening-detected and non-screening-detected AAAs (2.1% vs 4.5%, P=0.23).
Multivariable logistic regression (table XIX) shows an increased risk of death at 90 days for non screening-detected patients (OR 3.31, 95% CI, 1.05-10.46) when adjusted for age and method of intervention (EVAR or OR).

Validity of Screening Variable
Validation of 100 patients' screening data showed that four (n=4) patients were registered as having a population-based screening-detected aneurysm when it was not and one patient was registered as having a non screening-detected aneurysm when it was screening-detected. Thus, there was a 95% match when comparing a true population-based screening finding of AAA with the variable, "screening detected", in Swedvasc.

Table XV. Clinical characteristics and preoperative risk factors in screening-detected patients compared to non-screening-detected age-matched controls.

Clinical characteristics	Screening-detected n (%)	Non screening-detected age-matched controls n (%)	
All subjects			
Age (years)*	66 (65-70)	68 (66-72)	P<0.001
Diabetes	36 (10.7)	46 (12.5)	P=0.16
Ever-smoker	277 (90.5)	256 (90.8)	P=1.00
Cardiac disease	128 (38.1)	142 (44.7)	P=0.10
Previous TIA/stroke	39 (11.7)	48 (15.0)	P=0.25
Hypertension	252 (75.0)	247 (77.7)	P=0.46
Creatinine > 150 micromole/l	7 (2.0)	14 (4.0)	P=0.18
Pulmonary disease	64 (19.2)	72 (23.0)	P=0.25
Maximal AAA diameter (mm)*	59 (55-64)	59 (55-65)	P=0.43

AAA= Abdominal aortic aneurysm. TIA=Transient ischemic attack. Values in parenthesis are percentages, unless indicated otherwise; * Values are median (IQR). P-values are based on the Mann-Whitney test for age and maximal aneurysm diameter and Fisher's exact test (2-sided) for comorbidity variables and smoking.
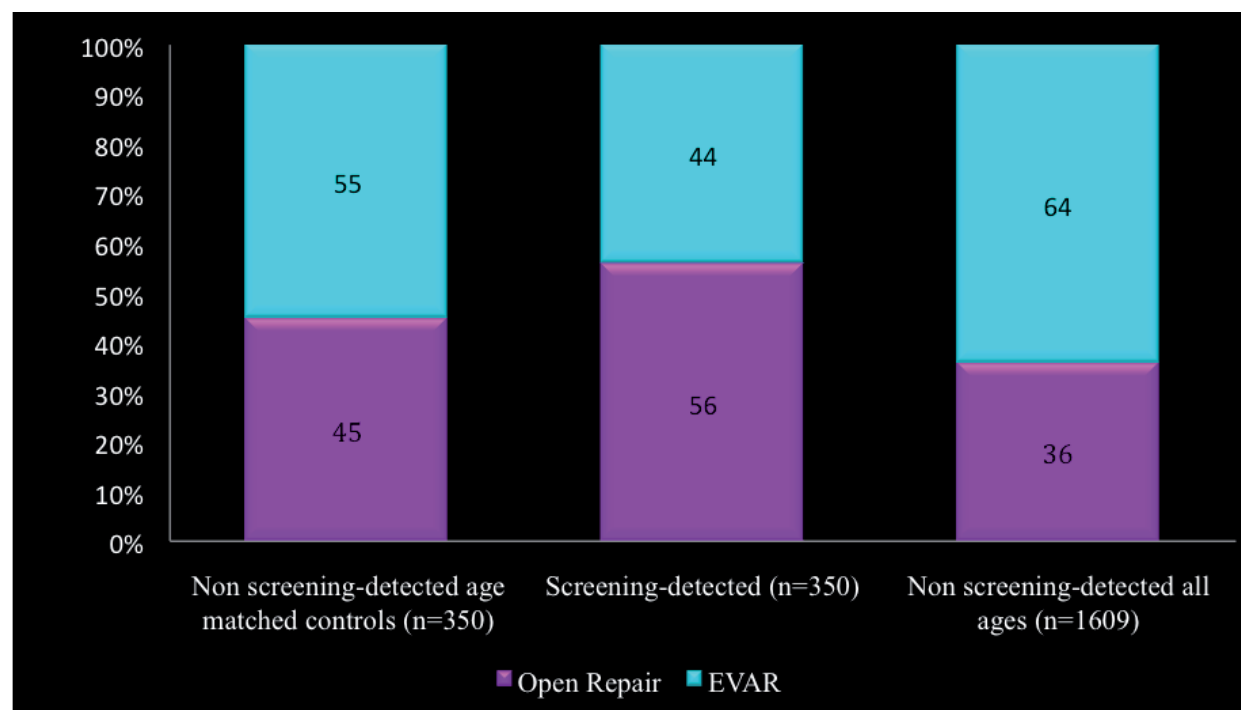
***Fig V.** Percentage of patients treated with EVAR or open repair in Sweden.*
From May, 2010, through January, 2013
Non screening-detected age matched controls compared to screening-detected P<0.01
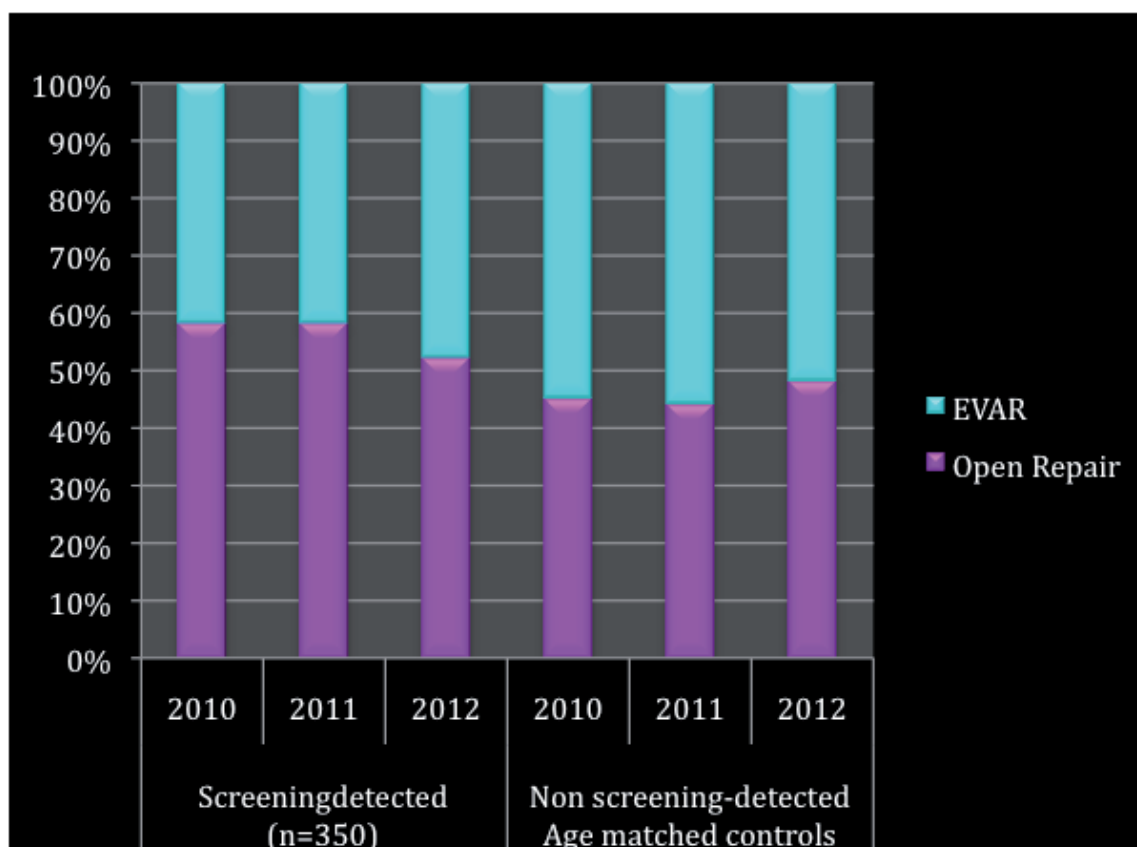*Non screening-detected all ages compared to screening-detected P<0.001*

Fig VI (*not in manuscript*) *Changes in choice of prophylactic surgery over time in Sweden*

Table XVI. Complications 30 days after surgery in screening-detected AAA patients compared to age matched controls. (n=663, 37 excluded due to missing data)

	Open repair			EVAR		
Complications 30 days after surgery	Screening-detected n (%)	Non-screening-detected age-matched controls n (%)	p	Screening-detected n (%)	Non screening-detected age-matched controls n (%)	p
	186	147		147	183	
Death	2 (1.0)	5 (3.2)	0.25	0 (0)	0 (0)	1.00
AMI	4 (2.2)	2 (1.4)	0.70	0 (0)	2 (1.1)	0.50
Stroke	2 (1.1)	3 (2.0)	0.66	1 (0.7)	1 (0.5)	1.00
Amputation	0 (0)	1 (0.7)	0.44	0 (0)	0 (0)	1.00
Bowel ischemia	1 (0.5)	1 (0.7)	1.00	0 (0)	0 (0)	1.00
Renal failure	7 (3.7)	8 (5.4)	0.60	2 (1.4)	5 (2.7)	0.47
*Combined endpoint**	*12 (6.2)*	*16 (10.2)*	*0.23*	*3 (1.9)*	*7 (3.6)*	*0.52*
Abd compartment	6 (3.2)	6 (4.1)	0.77	2 (1.4)	0 (0)	0.20
Distal embolization	5 (2.7)	5 (3.4)	0.75	2 (1.4)	2 (1.1)	1.00
Reop bleeding	2 (1.1)	4 (2.7)	0.41	1 (0.7)	5 (2.7)	0.23

AAA= Abdominal aortic aneurysm. AMI= acute myocardial infarction. EVAR=Endovascular aortic repair.
* Primary (combined) endpoint. Any of the following: death, AMI, stroke, major amputation, bowel ischemia, renal failure.

Table XVII. Odds ratio (OR) for primary endpoint consisting of any of the following: death, AMI, stroke, major amputation, bowel ischemia, renal failure within 30 days. Univariate (crude) and adjusted analyses. (n= 668, 32 patients excluded due to missing data)

Frequency and risk of death	Primary endpoint at 30 days* n (%)	OR Crude Primary endpoint	CI 95%	OR adj** Primary endpoint	95% CI
	n=668			n=668	
All	38			38	
Screening-detected	15 (4.3)	Ref		Ref	
Non-screening-detected (missing=0)	23 (6.6)	1.57	0.81-3.07	1.64	0.82-3.25
Open Repair	28 (8.0)	2.89	1.38-6.05	3.27	1.54-6.93
EVAR (missing=0)	10 (2.9)	Ref		Ref	
Age <68	15 (4.3)	Ref		Ref	
Age ≥68 (missing=0)	23 (6.5)	1.53	0.79-2.99	1.61	0.81-3.21
Hypertension, No	8 (5.2)	Ref			
Hypertension, Yes (missing=46)	28 (5.6)	1.12	0.50-2.50		
Diabetes, No	32 (5.6)	Ref			
Diabetes, Yes (missing=43)	4 (4.9)	0.85	0.29-2.48		
Creatinine <150	35 (5.2)	Ref			
Creatinine >150 (missing=0)	3 (14.3)	3.29	0.92-11.82		
Ever-smoker*	33 (6.2)				
Never-smoker (missing=112)	0				
Previous heart cond., No	12(3.1)	Ref			
Previous heart cond., Yes (missing=46)	24 (9.0)	3.10	1.52-6.33		
Respiratory disease, No	21 (4.1)	Ref			
Respiratory disease, Yes (missing=54)	15 (11.1)	2.88	1.44-5.76		
Previous TIA/Stroke , No	32 (5.7)	Ref			
Previous TIA/Stroke , Yes (missing=46)	4 (4.6)	0.80	0.28-2.32		

EVAR=Endovascular aortic repair. AMI= acute myocardial infarction. TIA=Transient ischemic attack.

* Primary (combined) endpoint including mortality, acute myocardial infarction (AMI), stroke, amputation, bowel ischemia, renal failure.

**Multivariable regression adjusted for screening-detection, method of intervention (OR and EVAR), age (<68, ≥68).

Table XVIII. Mortality after Open Repair and EndoVascular Aortic Repair (EVAR) in screening-detected AAA patients compared to non screening-detected age-matched controls.

	Open Repair (n=352)			EVAR (n=348)			All (n=700)		
	Screening-detected n (%)	Non screening-detected n (%)	p	Screening detected n (%)	Non screening-detected n (%)	p	Screening detected n (%)	Non screening-detected n (%)	p
n	195	157		155	193		350	350	
30-day	2/195 (1.0)	5/157 (3.2)	0.15	0/155 (0)	0/193 (0)		2/350 (0.6)	5/350 (1.4)	0.25
90-day	4/195 (2.1)	7/157 (4.5)	0.23	0/155 (0)	6/193 (3.1)	0.04	4/350 (1.1)	13/350 (3.7)	0.046
1-year	7/173 (4.0)	9/155 (5.8)	0.61	2/140(1.4	9/191 (4.7)	0.12	9/313 (2.8)	18/346 (5.2)	0.17

AAA= Abdominal Aortic Aneurysm

Table XIX. Odds ratio (OR) of death at 90 days after surgery. Univariate (crude) and adjusted analyses. (n= 699, 1 patient excluded due to missing data)

Frequency and risk of death	90-day mortality n (%) n=699	OR death 90-days crude	CI 95%	OR death 90 days adj* n=699	95% CI
All	17 (2.4)			17	
Screening-detected	4 (1.1)	Ref		Ref	
Non-screening-detected (missing=0)	13 (3.7)	3.33	1.07-10.31	3.31	1.05-10.46
Open Repair	11 (3.1)	1.83	0.67-5.01	2.23	0.80-6.20
EVAR (missing=0)	6 (1.7)	Ref		Ref	
Age <68 years	6 (1.7)	Ref		Ref	
Age ≥68 years (missing=0)	11 (3.1)	1.81	0.66-4.96	1.64	0.58-4.60
Hypertension, No	3 (1.9)				
Hypertension, Yes (missing=46)	13 (2.6)	1.36	0.38-4.85		
Diabetes, No	14 (2.4)	Ref			
Diabetes, Yes (missing=43)	2 (2.5)	1.01	0.23-4.53		
Creatinine <150	15 (2.2)	Ref			
Creatinine >150 (missing=0)	2 (9.5)	4.64	0.99-21.73		
Ever-smoker**	12 (2.3)				
Never-smoker (missing=112)	0				
Previous heart cond, No	6 (1.6)	Ref			
Previous heart cond, Yes (missing 46)	9 (3.4)	2.18	0.77-6.21		
Respiratory disease, No	9 (1.8)	Ref			
Respiratory disease, Yes (missing=54)	7 (5.2)	3.03	1.11-8.30		
Previous TIA/stroke, No	13 (2.3)	Ref			
Previous TIA/stroke, Yes (missing=46)	3 (3.4)	1.51	0.42-5.42		

*Multivariable regression adjusted for screening detection, age and method of intervention (OR and EVAR).
**Current or previous smoker.

5. DISCUSSION

The projects presented in this thesis aim at improving detection of AAA in the population and to study the outcome of treated patients detected through screening. Many doctors worldwide have worked hard to show the benefit of, and lately to implement, population-based screening. Their efforts have resulted in screening programs for men in several countries. Since screening is now implemented in almost all counties in Sweden it is time to take the next step, and focus on detecting AAA's in the groups of persons that are not invited to screening and those not participating in screening.

5.1 Screening of siblings

One tenth of siblings to AAA patients have AAA, this prevalence rate is almost seven times higher than in the population based screening program for men (10 % vs 1.5%).

One group with a very high frequency of AAA is first-degree relatives to AAA-patients.[17] The result from study I in this thesis, showing that only 11% of participating siblings had been subject to examination of their aorta prior to participating in the study indicate that not enough siblings are screened.

The prevalence of AAA in siblings younger than 80 was 17% in brothers and 6% in sisters. In our cohort of 529 examined siblings from study I and II we found a total AAA-prevalence of 10%. (table IX). It is likely that the prevalence would be higher if siblings >80 were included since high age is one of the strongest risk factors for AAA. The prevalence should be compared to that from population-based screening in Sweden, 1.5-2.2%. Brothers to AAA-patients will be invited to screening at age 65, but our results in study II indicate that this is not sufficient for all since 8/16 (50%)of the large AAA's we found were in siblings younger than 65 (table XI). Sisters will not be invited to population-based screening and have a larger risk of remaining undiagnosed.

We have an active outreach to screen 65-year old men, and we have the means to find siblings in Sweden in terms of family-registers. An improved identification system to selectively invite and screen FDRs to AAA patients is likely to be cost efficient, considering the expected high prevalence. It is obvious that the present random information system to patients and their FDRs regarding heredity of AAA is insufficient and unequal, since it depends on chance what doctor and at which hospital you are treated. This more systematic approach would increase the possibility to obtain "equal "health regardless of gender, age or region.

At what age should we screen siblings for AAA?
There is, with this thesis and other studies, plenty of evidence that FDR to AAA-patients are at high risk of AAA.[17, 61, 63, 149, 150] A commonly raised question is at what age the sibling should be screened and the recommendations regarding screening for AAA in FDR to AAA-patients vary. The Society for Vascular Surgery (SVS2 recommendations) recommends screening of men >55 with a FDR with AAA. The recommendation regarding women is screening at age 65 if they have an affected FDR or have ever smoked.[92]

Of the siblings with AAA in study I and II, 32% were diagnosed before age 65 and 16% had aneurysms >5cm before age 65. The findings of several young siblings with AAA, in this study and other's, indicate that age 65 not is an optimal time to screen siblings (table XI). [17, 62, 64, 65, 71-73, 151] The fact that we found young brothers with large AAA's indicate that population based screening at age 65 is not safe for siblings. As a suggestion, it would be reasonable to screen sisters at the age of 55, and brothers at the age of 50. Re-screening at a higher age is probably motivated for siblings with a normal aorta but we have no data to support this in our studies.

What about children to AAA-patients?
One can hypothesize that our findings regarding prevalence are applicable to children of AAA-patients, but this is not investigated in our material. The suggestion of a systematic invitation to screening should, by reason, include children as well as siblings. However, this raises new practical and ethical difficulties since the child of an AAA-patient probably is at low risk of disease at the time-point of AAA-detection in their parent, because of young age.
A formal registry for FDR to AAA patients could be systematized with an informed consent process. Or, as an easier version, a letter could be sent to all siblings informing them of the need for screening at a certain age.
Considering the high cost-benefit of screening elderly men reported, and the ethics analyzed in this context, a similar process for FDR would be highly relevant and called for.

5.2 No regional differences in AAA-prevalence in siblings

The prevalence of AAA in the general population is higher in the North of Sweden and so is the incidence.[76] The reported higher prevalence in the North is not explained by our findings in study II regarding a different hereditary pattern in the investigated affected families.
Other reasons for the geographical differences may also be considered, such as smoking, but according to statistics from the "Public Health Agency of Sweden" smoking is not more common in the North region, and would subsequently not be responsible for the difference in risk (table XX).[77]
There is evidence that the population in the North have higher levels of cholesterol and that they consume more statins.[60, 78] High cholesterol-levels are closely linked to cardiovascular disease but in fact, regarding AAA, only low levels of high-density-lipoproteins (HDL) are shown to be associated with increased risk of disease, not high levels of low-density-lipoprotein (LDL).[152] Further studies are needed before any conclusion can be drawn that the different regional AAA prevalence rates are correlated to differences in the lipid profiles.
High alcohol-consumption seems to have different effects on risk of AAA depending on gender, but according to available statistics from "Public Health Agency of Sweden" alcohol-consumption is not higher in North compared to Mid Sweden.[77, 153]
The many latitudes that Sweden covers lead to large regional differences regarding daylight and temperature; winters in the north of Sweden offer very few hours of daylight. Vitamin D deficiency is reported to increase with high latitudes in Caucasians.[154] The recent data showing that vitamin D deficiency is linked to cardiovascular disease as well as AAA are interesting.[155,80] There are no available data on the effect of Vitamin-D substitution on AAA.

There were more siblings participating from each family in the North region (study II) compared to mid (Study I). Data from "Public Health Agency of Sweden" confirm that the average number of siblings is higher in the North region. Since the prevalence of AAA is higher in the north part of Sweden, and the prevalence of AAA among siblings to AAA-patients is higher than in the general population, the larger family size in northern Sweden could constitute a possible explanation of the higher prevalence of AAA in the general population in north.

Table XX. Statistic data from the general population. Diagnoses from inpatient directory Mid Sweden (Stockholms län) and North Sweden (Norrbottens län).[35, 37] Average number of patients/100 000 inhabitants treated for disease 1998-2012, all patients >40 included

	Mid	North
Mean Age of general population	39.0	43.5
Abdominal/thoracic aneurysm		
Age 40-44	3	4
Age 45-49	5	3
Age 50-54	10	11
Age 55-59	16	28
Age 60-64	33	56
Age 65-69	63	100
Age 70-74	109	146
Age 75-79	135	194
Age 80-84	140	180
Age 85+	98	140
IHD	860	1344
Ischemic Stroke	431	508
COPD/asthma	249	338
Atherosclerosis/thrombotic/embolic disease, peripheral arteries	144	198
Diabetes	175	310
Statins*	403	499
Self-reported smoking 2010-2013**		
Never smoker	59%	59%
Ex smoker	18%	17%
Current smoker	24%	23%

IHD=Ischemic heart disease, COPD=Chronic Obstructive pulmonary disease
* Number of daily doses retrieved from pharmacies/100 000 inhabitants
**Self-reported, Ages 16-84

5.3 Participation in population-based screening

A striking correlation between a poor socioeconomic status and a low participation rate in screening was found in the Stockholm screening program. Few modifiable risk factors could be identified.

The results from this cohort study of 24139 men invited to screening, showed that the participation rate was influenced by income, education, immigration-status, marital status and travel distance. The non-participants had different comorbidity profile compared to participants indicating that they suffer an at least equal risk for AAA-disease compared to the participants, if not higher.

The mean participation-rate of 77.6% in the Stockholm AAA screening program is at large consistent with the participation rates in England (75%)[156] and Malmö Sweden (80%)[157], but somewhat lower than other regions in Sweden Uppsala (85%)[44] and Scotland (90.1%)[158], and much higher than others.[143] It is indeed troublesome that the participation rate is very low at 50-60% in some of the socioeconomic groups that would probably benefit most from screening since their frequency of aneurysms is high (tables XII and XIII).

It has been reported that the mortality rate and possibly the health status could differ for non-participants compared to participants. In the Chichester-trial the non-participants in the group invited to screening had a much higher 5-year all cause mortality (19.5%) than the controls not invited to screening (12.5%).[52] This led us to investigate if non-participants in AAA-screening have a higher morbidity than participants. In table XIV we show the comorbidity of the persons invited to screening, revealing a somewhat higher frequency of most diagnoses in the non-participant-group with the exception of malignancies. This is consistent with the mortality data from the Chichester-trial and support, together with smoking data, the theory that there are also more AAA's to be found in the non-participant group.

The data show that a lower percentage of the participants in screening have been admitted to hospital >2 times in the past 10 years prior to screening (29.1% vs 32.9%) table XIV. At the same time, a higher percentage of the participants have visited outpatient specialist centers >2 times compared to the non-participants (85.1% vs 76.3%).

The lower percentage of outpatient visits in the non-participant group could be caused by the fact that non-participants to a lesser extent participate in prophylactic health care, and as a result to a higher extent need in-hospital care.[159]

The effect of the removal of the patient-fee during the latter part of the study period on participation rates is not yet possible to analyze, but the effect of increased participation could be anticipated based on other reports [160, 161]. In the meta-analysis by Stone et al financial incentives was one of the strongest factors contributing to an increased participation-rate in breast-, cervix- and colon cancer screening.[161]

Prevalence of AAA in population-based screening in Sweden

The prevalence of AAA in the 65-year old men in study III was 1.4%, which is lower than expected but in accordance with recent reports from England and Sweden.[44, 156, 157]

This low prevalence can possibly be attributed to decreased smoking. The smoking rate in men (65-74 years of age) has decreased from 32% 1977 to 13% 2009 in Sweden.[77]

Improving the participation rates in the population-based screening
Some factors important for non-participation in study III must be considered non-modifiable i.e. income, educational level and marital status. The data reveal that immigrants and those with very long travel distance are groups with modifiable factors available for improved screening. These groups might also have poorer outcome in case of a rAAA due to long travel-distance and communication problems.

The participation rates are low for all immigrants and especially those who immigrated more recently. The fact that the adjusted participation rate is higher for immigrants having spent longer time in Sweden compared to those recently immigrated implies a possible language-barrier in this group, but other factors i.e. cultural differences could also be important.[157] The low participation rate could possibly be overcome by giving the invited men access to information in their native language, or maybe by adding more describing pictures. Local information campaigns in municipalities where immigration-rates are high are currently investigated in the south of Sweden.

The travel-distance data reveal a lower participation rate in the group with a distance >31km to travel to screening center (table XIII). This is consistent with data from some other studies[140, 162-164], but not with others.[157, 165] In our study, persons that have a long travel-distance to a high extent live in rural areas. Persons living in rural areas have a higher participation rate in other screening-studies, therefore their lower participation rate in this study is somewhat intriguing.[139, 165] The effects of offering screening more close to the home could be investigated in terms of cost/benefit. A recent study from Malmö, Sweden, showed an increase in participation-rate with a local information campaign.[157]

5.4 Results of surgery on screening-detected AAA's

The most important finding of this nationwide population-based study of AAAs is the overall low postoperative morbidity and mortality in this cohort of screening-detected patients and controls. The 30-day mortality for the entire group was only 1% and the 1-year mortality 4.1%. Between screening-detected patients and non-screening detected controls we found no difference in comorbidity, 30-day mortality, 1-year mortality or major adverse events.
Few countries have population-based screening and national vascular registries. There is a window of opportunity to investigate the outcome in screened men compared to non-screened men. In 2-3 years very few non-screened men will be treated electively for AAA. The very low event rate decreases the possibility to perform in depth statistical comparisons between non-screened and screened men. The lower 90-day mortality among the screening-detected men, compared to the age-matched controls indicates a lower surgical risk, but caution in the interpretation is warranted due to the higher age of the controls.

When comparing short-term mortality after AAA-surgery with that in other studies, the EVAR/OR-rate needs to be considered, since EVAR has a lower short-term mortality. A report from the United Kingdom, with a proportion of EVARs similar to that in this cohort (45%), has shown a correspondingly low 30-day mortality for their screening-detected AAA's (UK, 1.6%; Sweden, 0.6%).[156] Another contemporary comparison could be made with the randomized ACE-trial which also had a low 30-day mortality after OR and EVAR

(0.6% and 1.3%).[94] Both groups in this current study are younger than any average AAA cohort, which contributes to the low mortality. The recently reported low 30-day mortality in this study and the above mentioned probably reflects the relatively young cohorts and an increasing rate of EVAR, but it could also be an effect of centralized surgery, improved perioperative care, and less comorbidity.

No differences in preoperative comorbidity but screening-detected are treated with OR to a higher extent

Before AAA screening started, almost all electively treated AAA's were detected coincidentally, in patients who had sought medical advice for a symptom, and were therefore more likely to have a coexisting disease. In theory, it is likely that screening-detected patients would have coexisting diseases to a lesser extent. Importantly, we did not find the anticipated differences in pre-existing comorbidities between the screening-detected and the age-matched non-screening-detected group. This may also be the reason that we did not find significant differences in outcomes (except for 90 day mortality). Despite the lack of any detected difference in comorbidity, there is a rather large difference in the methods chosen for aneurysm repair. Screening-detected patients have been treated with open repair in 56% of cases, compared to 45% in the non-screening-detected cases. This does probably reflect a preconceived notion that screening-detected patients are healthier than others and would tolerate open surgery better. The treating vascular surgeons choose the method of prophylactic treatment (OR or EVAR) and the Swedvasc registry does not include data regarding reasons for the choice.

In this cohort of men undergoing elective repair of an AAA, only 18% were screening-detected. Since the screening programs in Sweden started regionally in 2006 and then were gradually implemented, the non-screening-detected cohort in this study probably consists mainly of patients who have not been offered AAA-screening. In coming years there will be no cohort of non-screened like this available in Sweden among men since screening will find most of the persons with AAA.

Risk of rupture and size at which to offer prophylactic surgery in young patients

Screening-detected and non-screened young men have a very low postoperative mortality in this contemporary data and we did not find large differences between the groups. When viewing study IV in a more descriptive aspect, surgery on younger patients seems to, not unexpectedly, be associated with a lower complication rate. This could be compared to the rupture-rates from the UK-SAT -trial and the ADAM-trial with the conclusion that there might now be reasonable to offer surgery at a smaller AAA-size of perhaps 5.0 cm in young patients.[166, 167] However, fresh data regarding risk of rupture show that this also has declined (in men), possibly due to less smoking and better medical secondary prevention.[83] In study IV we excluded women since there is no population based screening in women in Sweden. However, one third of patients treated in hospital with AAA-diagnoses in Sweden 2012 were women (table III). There are studies showing worse outcome after surgery on women compared to men but the high annual risk of rupture of 3% in 5 cm AAA is very high as well. A lower threshold of 5 cm for offering prophylactic surgery to women seems reasonable and is now implemented in Stockholm. While in-hospital registries show that 30% of in hospital-treated with AAA were women, Swedvasc data from the same year show that among those surgically treated only 16% were women.

5.5 Future perspectives

Organized screening of siblings and offspring to AAA-patients
As mentioned above, a project where we study the feasibility of organized screening of FDR's to AAA-patients would be the first step towards implementing an organized screening-program. This is a patient-group with an extremely high risk to develop disease. It is possible that this would save more lives at a lower cost than the population based screening.

Improving participation in population-based screening
The effects of offering screening more close to the home should be investigated in terms of cost/benefit. A randomized trial in counties with long travel-distance, offering half the population screening closed to their home would be preferred.
In the same fashion the effects of multilingual invitations and information should be studied.

Is HS-CRP a predictor that can be used to decide which patient with small AAA safely can refrain from statins?
After a long era with inconclusive data regarding benefit of long-term medical secondary prevention and small AAA's, recent studies have convinced us that at least statins are of benefit for patients with small AAA's. However, many patients suffer from troublesome side effects when using statins, and finding a drug and a dose that can be tolerated is sometimes difficult. A recent study used HS-CRP as a marked for cardiovascular disease in AAA-patients. We learned that 48% of patients with AAA, even without symptoms of cardiovascular disease, are at high risk of cardiovascular events.[168] It would be clinically useful to know which AAA-patient safely could refrain from statins and in which patient we must make every effort to find a tolerable lipid-lowering treatment.

Personal reflections regarding heredity and AAA's: Are all aneurysms alike?
In 2008 we started the small-aneurysm dispensary at Södersjukhuset, which offer outpatients a clinical evaluation and an ultrasound scan at the same occasion. This has given us the opportunity to scan many AAA's. It is noticeable that some have a large amount of calcification while some have none at all. A personal reflection is that those without calcification to a larger extent have multiple aneurysms. Intrigued, one can wonder if there are two types of aneurysms, those originating from calcification and those who don't. The aneurysms with calcifications have been shown to grow more slowly.[169] A recent study from Japan showed that AAA in patients with a family history grew more rapidly.[170] It would be truly interesting to study if there is a difference in heredity and perhaps genetics between those groups.

5.6 Strengths and limitations

Studies I and II
Strength:
- All ultrasounds were performed by two investigators (Linné and Forsberg), both trained at a central core facility in Stockholm.

Limitations:
- The information regarding siblings was self-reported from the patients with AAA, not extracted from the national family-register. It is possible that all siblings not were reported. For instance, a sibling with social- or abuse problems might not get mentioned.
- The age-limit of 80 years was set to avoid the ethical dilemma of finding AAA's in patients not suitable for prophylactic surgery. This, almost certainly, generates an inclusion bias. A higher age-limit would have generated a higher prevalence of AAA. As such, we cannot claim that our found prevalence of AAA in sibling is a true prevalence of the entire sibling-population. *This leads to a falsely low prevalence in our results*
- The decision to only include siblings still living in same region is a potential inclusion bias since there is a chance that siblings transferring to other regions could have a different risk of disease. Most likely people with a higher level of education would be more prone to transfer. *If this is the case it leads to a falsely high prevalence in our results.*

Study III
Strength:
- In the conduction of study III individual data was used. This is novel compared to previous registry-based studies, which have regarded risk factors on a group level. This gave us the opportunity to make reliable multi-variable analysis.

Limitations:
- Smoking data was not available on an individual level. This information would have added much to our study since it is a likely confounder to at least level of education and income, possibly immigration-status as well.
- Power: When analyzing such a large cohort as 24.000, statistical significance is easy to find. The analysis of health-care revealed that 29.1% of the men participating in screening had >2 in-hospital admissions within the past 10 years before invitation to screening, compared to 32.9% in the non-participant group (p <0.0001). This is an example of a statistical highly significant finding where however the clinical relevance in differences in 3%-units can be discussed.

Study IV
Strength:
- The Swedvasc registry is validated with good results. The Registry has been found to have a 93.1% external validity for registration of abdominal aortic aneurysms (AAAs).[146, 147] In this study we validated the "screening-detected" variable and found a 95% validity.

Limitations:
- Power: The good results of surgery in this young cohort gave us a limited number of outcomes. The presence of a type II error cannot be excluded.
- Due to the lack of non-screening detected controls available for age-matching we needed to allow for a age-span of two years to find enough controls, resulting in a unfortunate age-difference between the groups. However, if we were to repeat the study in a year the chance of finding controls would probably be even smaller.

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