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# Screening for Abdominal Aortic Aneurysm

SVERKER SVENSJÖ



ACTA  
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UPPSALA  
2013

ISSN 1651-6206  
ISBN 978-91-554-8668-6  
urn:nbn:se:uu:diva-198677

Dissertation presented at Uppsala University to be publicly examined in Föreläsningssalen, Falu Lasarett, Entré 6:C 01, Söderbaums väg 8, Falun, Friday, June 7, 2013 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English.

### **Abstract**

Svensjö, S. 2013. Screening for Abdominal Aortic Aneurysm. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 903. 82 pp. Uppsala. ISBN 978-91-554-8668-6.

Randomised controlled trials have demonstrated that mortality from Abdominal Aortic Aneurysm (AAA) can be cost-effectively reduced by ultrasound-screening of men. Evidence for screening women is insufficient. Reports of falling AAA incidence are emerging.

In an effort to study screening for AAA in a contemporary setting, two cross-sectional multi-centre population-based studies of one-time screening of 65-year-old men, and 70-year-old women in Middle Sweden were undertaken. Cost-efficiency of one-time screening of 65-year-old men was evaluated in a decision-analysis model. Five-year outcomes in men invited to screening at age 65 and age 70, were studied in a longitudinal cohort study.

A lower than expected (1.7%) prevalence of AAA in 65-year-old men was found, as well as a very low (0.4%) prevalence in 70-year-old women. Smoking was the dominating risk factor associated with AAA, but the association was stronger in women. The main cause of reduced contemporary prevalence was falling smoking rates in the population since 30 years.

One-time screening of 65-year-old men was found to be cost-effective and deliver significant clinical impact. The cost per quality adjusted life-year gained, at 13-years follow-up, was €14706, which was below the recommended UK NICE threshold of €25000. 15 lives were saved by inviting 10000 to screening. Prevalence of AAA and the rate of incidental detection of AAAs in the population were important factors affecting cost-efficiency.

New AAAs developed after 5 years in men screened normal at age 65, predominantly in men with sub-aneurysmal aortas (25-29mm) at 65, and smokers. The 5-year rate of AAA repair was high among men with screening detected AAAs, as was non-AAA related mortality. Ruptures were only documented among non-attenders.

Conclusions: A lower than expected prevalence of AAA among 65-year-old men, an unchanged repair rate, and improved longevity of the elderly population was found. Although one-time screening for AAA was still cost-effective within a contemporary context, several issues need to be addressed; the threshold diameter for follow-up, the current rate of opportunistic detection of AAA in the population, re-screening of the entire population at a higher age, and targeted screening of smokers. Screening 70-year-old women who do not smoke is likely to be futile, thus ruling out population screening of women for AAA.

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ISSN 1651-6206

ISBN 978-91-554-8668-6

urn:nbn:se:uu:diva-198677 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-198677>)

*To Lena, Joel, Emil and Anton*



# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Svensjö, S, Björck, M, Gürtelschmid, M, Djavani-Gidlund, K, Hellberg, A, Wanhainen A. Low prevalence of abdominal aortic aneurysm among 65-year-old Swedish men indicates a change in the epidemiology of the disease.  
*Circulation*, 2011;124(10):1118-1123
- II Svensjö, S, Björck, M, Wanhainen A. Current prevalence of abdominal aortic aneurysm in 70-year-old women.  
*Br J Surg*, 2013;100(3):367-372
- III Svensjö, S, Mani, K, Björck, M, Lundkvist, J, Wanhainen A. Screening for Abdominal Aortic Aneurysm in 65-year-old Men remains Cost-effective with Contemporary Epidemiology and Management.  
*Submitted Manuscript*
- IV Svensjö, S, Björck, M, Wanhainen A. Five-year outcomes in men screened for abdominal aortic aneurysm at 65 years of age, a population-based cohort study  
*Manuscript*

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# Abbreviations

AAA	Abdominal Aortic Aneurysm
CT	Computerised Tomography
EVAR	Endovascular Aneurysm Repair
HR	Hazard Ratio
LELE	Leading Edge to Leading Edge
MRI	Magnetic Resonance Imaging
O.R.	Odds Ratio
ODR	Opportunistic Detection and Repair Rate of AAA
OR	Open Repair
QALY	Quality Adjusted Life-year
RCT	Randomised Controlled Trial
Swedvasc	The Swedish Vascular Registry
US	Ultrasound/Ultrasonography



# Introduction

In this thesis, aspects of screening for Abdominal Aortic Aneurysm (AAA) in a contemporary setting are analysed. In particular, today's occurrence of the disease and its association with risk factors in men and women are approached. In addition, the costs and impact of AAA screening in a modern epidemiological setting are evaluated. Lastly, the outcome after 5 years in a group of individuals screened for AAA is studied.

In the following paragraphs of this introduction, key characteristics of the disease are presented, and some general aspects on AAA screening are discussed. In the last paragraphs of the introduction, a brief summary of some areas within this field of research where information is lacking is presented.

## Abdominal Aortic Aneurysm

An arterial aneurysm is a localized widening of the arterial wall. It is caused by a degenerative process, in which degradation of the connective tissue proteins elastin and collagen in the arterial wall is a key element (Sakalihasan 2005, Nordon 2011). An abdominal aortic aneurysm (AAA) is an aneurysm affecting the abdominal part of the aorta, most commonly the infra renal segment. An AAA is commonly defined as a maximum infrarenal diameter of 30mm or more as demonstrated with US, CT or MRI (McGregor 1975, Moll 2011). However, there is no universally accepted definition of an AAA. Other definitions include an infrarenal aortic diameter of at least 1.5 x the suprarenal aortic diameter (Sterpetti 1987, Johnston 1991). It is, however, evident that contemporary studies uniformly include 30mm or more in infrarenal aortic diameter as the diagnostic criterion for an AAA (Wanhainen 2008).

The exact pathophysiological mechanism of AAA development has not been determined. Several factors have been shown to increase the risk of having an AAA, the dominating risk factors being male gender, age, smoking, heredity and presence of one or more cardiovascular risk factors (MacSweeney 1994, Lederle 1997).

The natural history of an AAA is to slowly expand (Glimaker 1991, Lederle 2002, Noronen 2013). The expansion rate is difficult to predict on an individual basis (Sterpetti 1987). It has, however, been determined that larger AAAs expand more rapidly and factors such as smoking also accelerate

the growth pattern (Lindholt 2001, Thompson 2010, Powell 2011, Sweeting 2012).

AAA is a predominantly silent disease in which the most common, as well as catastrophic, symptom is rupture. The yearly risk of rupture increases with the aneurysm diameter, and the risk is negligible up to approximately 5cm, where after it steadily increases to reach a level of 30% or more at 7cm (Lederle 2002, Brown 2003, Brady 2004). This emergency condition with sudden, massive internal bleeding is associated with a total mortality of approximately 80% (Bergqvist 1994, Von Allmen 2012). Thus, a substantial proportion of patients suffering a rupture die suddenly without reaching the hospital, and of those reaching the hospital some die awaiting diagnosis or treatment. Of those reaching the operating room, approximately 30% die during or shortly after surgery (van der Vliet 1997). Emergency surgery to repair a ruptured AAA is a technically challenging procedure in which the outcome in many cases is uncertain, and the obligatory subsequent intensive care is costly and resource-demanding. In addition, serious permanent complications, such as intestinal gangrene, renal failure, and spinal ischemia are more common after surgery for rupture. In comparison, carefully planned elective surgery for a non-ruptured AAA is today a relatively safe procedure that in many cases can be performed with a mortality of approximately <2% and low degree of postoperative morbidity (Wanhainen 2008, Greenhalgh 2010, Mani 2011, Lederle 2012).

Asymptomatic AAAs are usually detected incidentally by abdominal palpation, or more commonly as an incidental finding on a radiological examination directed at another disease.

After detection of an AAA, regular ultrasound surveillance to monitor expansion is advised. The decision to operate an AAA depends largely on the maximum diameter of the AAA, the patient's fitness for surgery, and the expected longevity (Grant 2013). In two large randomized trials, the UK Small Aneurysm Trial (UKSAT), and the American Aneurysm Detection and Management study (ADAM), ultrasound surveillance of AAAs of 4.0 up to 5.5cm, was equivalent to early surgical intervention (UKSAT 1998, Lederle 2002, Powell 2007). In the studies, surgical intervention was considered at AAA size of 5.5cm or more, after rapid expansion (1cm/year) or for symptomatic aneurysms. A widely adopted view is that patients with AAAs that have reached 5.5cm or more in maximum diameter should be referred to a vascular surgeon for optimisation of medical treatment and consideration of surgical repair (Moll 2011). The threshold for consideration of surgical intervention in women should be lower due to higher rupture rate at equal AAA size, most likely to 4.5-5.0cm. (Chaikof 2009).

Once the need for surgical repair has been determined, the surgeon will choose between conventional open repair (OR) or endovascular repair (EVAR). In open repair the abdomen is opened with an incision under general anaesthesia, the infra renal aorta is then clamped temporarily and the

AAA replaced with a synthetic flexible vascular prosthetic (graft) that is manually sutured to the aortic wall. In endovascular repair, the AAA is repaired by relining the infrarenal aorta with a synthetic fabric attached to a flexible metal skeleton (stent graft). Under x-ray guidance, the stent graft is deployed inside the aorta at the correct location by inserting it via catheters placed in incisions in the arterial vessels in the groin. This procedure can be performed in local, regional, or general anaesthesia. Since its introduction in the 1990:s, the endovascular method has steadily gained ground, and now accounts for more than 50% of AAA repairs in Europe (Mani 2011), in some centres >90%. Elective AAA repair is associated with a 30-day mortality, three times higher for OR (4.7%) than for EVAR (1.7%), as established in the EVAR 1 and DREAM trials (Greenhalgh 2004, Prinssen 2004). The long-term mortality displays no difference, however (De Bruin 2010, Greenhalgh 2010, Lederle 2012, Stather 2013). The choice of OR or EVAR ultimately depends on several factors, such as the experience of the treating vascular surgeon, the health-care setting the patient is referred to, anatomical suitability for either method, patient comorbidities and patient preference (Rutherford 2008).

## Epidemiology

*“Epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants”* (World Health Organisation 2011).

### **Prevalence**

Population-based screening studies provide the best available data on AAA disease prevalence (Moll 2011). In addition, valuable data on historical prevalence is the result of necropsy studies (Bengtsson 1992). Until just a decade ago, prevalence rates of approximately 4-9% among elderly men were frequently reported (Simoni 1995, Wilmink 1999, Lederle 2000, Ashton 2002, McCarthy 2003, Lindholt 2005). Also, an indication of a trend of increasing prevalence of AAA was demonstrated at this time (Melton 1984, Lilienfeld 1987) as well as increasing rupture rates up until the early 2000's (Acosta 2006).

Recently, however, reports signalling lower disease occurrence have emerged (Norman 2011, Sandiford 2011, Anjum 2012, Darwood 2012), as well as from accumulating screening data from the NHS Abdominal Aortic Screening Programme in England (NAAASP) now reporting prevalence rates of approximately 1.5%.

## **Risk factors**

Numerous reports have analysed risk factors for AAA. Age is associated with AAA, and advanced age increases the risk of AAA (Bengtsson 1992, CASS 2001, Forsdahl 2009), with AAAs being uncommon below the age of 60. Individuals with a 1st degree relative with AAA are at an up to 8 times increased risk of developing an AAA (Ogata 2005, Wanhainen 2005, Larsson 2009). Gender highly influences the risk of AAA, with the ratio of women to men displaying AAA disease commonly reported as 1:4-6 in age matched populations (Vardulaki 2000, Scott 2002, Derubertis 2007). A history of other vascular aneurysms increases the risk of AAA (MacSweeney 1993, Ravn 2007), and an AAA is also associated with increased risk of a thoracic aortic aneurysm (Larsson 2011). Ethnicity also seems to influence the occurrence of AAA disease with black men, and men of Asian origin having reduced risk of AAA disease (Wilson 2008, Salem 2009). Recently abdominal adiposity was reported to increase the risk of AAA (Stackelberg 2013). In contrast, Diabetes Mellitus displays a negative association with AAA (Lederle 1997). In a comprehensive review of risk factors for AAA, a weighted mean of risk factor distribution in over 110 000 subjects in screening studies; coronary artery disease, hypercholesterolemia, and hypertension also displayed clear associations with increased risk of AAA (Golledge 2006).

### *Smoking*

Of all risk factors that are possible to influence by the individual, smoking is the altogether dominating risk factor associated with the development of an AAA. In the literature, smoking is consistently associated with increasing risk of AAA (Lederle 2000, Singh 2001, Wanhainen 2005), as well as increasing AAA growth and increasing the risk of rupture (Brown 1999, Sweeting 2012). It can be estimated that smoking is the cause of 75% of AAA cases (Lederle 2000). It is also likely that smoking is the cause of the higher total mortality rates suffered by individuals with small AAAs, in the way that individuals with AAA to a higher degree suffer from associated cardiovascular conditions, such as coronary and cerebrovascular disease (Newman 2001, Freiberg 2008).

Smoking cessation leads to decreased risk of rupture, most likely through reduced growth rate (Brown 1999). Thus, in addition to surgical treatment of large AAAs, smoking cessation therapy and modification of other risk factors is most likely an equally important treatment among these individuals. A recent study has indicated that adequate smoking cessation intervention in patients with small AAAs identified at screening can cost-effectively increase long-term survival and decrease the need for AAA repair (Mani 2011).

## Vascular ultrasound, arterial duplex scanning

Duplex ultrasound is an invaluable component in the diagnosis of vascular disease, including assessment of arterial aneurysmal disease. Duplex refers to the combination of B-mode ultrasound and real-time Doppler flow imaging. The B-mode grey-scale image depicts the tissue and gives a two-dimensional cross-section of the vessel anatomy. The real-time color-flow Doppler imaging results in a color-coded depiction of the arterial blood flow superimposed on the B-mode image.

In addition, a spectral Doppler measurement can be made to assess the specific flow velocity in a chosen sampling point in the arterial lumen at a specified angle to the direction of the blood-flow. The former Doppler mode supplies information on the general distribution of blood-flow velocities in the lumen, whereas the latter provides a quantitative result with a specific velocity in a specific sampling point. The various sampled velocities are the basis for determining the degree of stenosis in the artery at the sampling point. The higher the velocity, the higher the degree of stenosis.

Duplex ultrasound is safe and non-invasive and provides a real-time image of the region of interest, that can be continuously modified by the technician to display the lesion from different perspectives and the chosen segment of the arterial vessel (Armstrong 2010).

Ultrasound is a fast, inexpensive, and non-invasive technique to depict AAAs in screening programmes and surveillance programmes. Duplex scanning also has high sensitivity and specificity for detection of AAAs (Lederle 1988, Lindholt 1999).

## Screening

In medicine, screening is a method to detect an asymptomatic disease in a population with the use of a test. Contrary to many other actions in health care, the test is offered to apparently healthy individuals or entire populations in the community. The intention of screening is to detect a disease at an early stage, in the hope of thus delivering a more effective treatment than had the disease been allowed to progress. Universal or general screening involves examining of all individuals within a certain category (for example all men 65 years of age). Targeted screening or case-finding involves examining a selection of individuals based on presence of a risk factor (such as women with a history of smoking or a known cardiovascular condition). Several successful examples of screening in medicine are available; screening for breast cancer with mammography, PPD-screening for tuberculosis, and using pap-smear for early detection of cervical cancer.

### **AAA screening**

AAA is a disease exceptionally well suited for screening, and ultrasound-based AAA screening fulfils all of WHO's basic criteria for a medical screening program (Wilson 1968). Mainly, it represents a significant health problem in elderly, a suitable rapid, safe, and accurate screening method is available, the natural course is well established with a long latent stage, in addition to effective treatments being readily available in modern health care settings. Lastly, mortality from rupture is extremely high and pre-emptive surgical treatment in properly selected individuals prevents premature death and the surgery can be performed in a cost-effective manner and is already an established and accepted treatment in modern societies.

Since the report from the first population-based screening study (Collin 1988), four influential randomised controlled trials of population screening have been launched, and delivered long-term follow-up data, Table 1. They are the Chichester trial in the UK (Scott 1995), the Viborg Trial in Denmark (Lindholt 2002), the Western Australia trial (Norman 2004), and the Multi-centre Aneurysm Screening Study [MASS] in the UK (Ashton 2002), representing over 137000 randomised individuals.

Table 1. *Overview of the randomized population-based screening trials.*

Characteristic	Chichester, UK	Viborg, Denmark	MASS, UK	Western Australia
Number randomised	15,775	12,628	67,800	41,000
Gender	Men & Women	Men	Men	Men
Age (years)	65-80	65-73	65-74	65-79
Recruitment	1988-1990	1994-1998	1997-1999	1996-1998
First published	1995	2002	2002	2004
First follow-up	2.5 years	5.1 years	4.1 years	3.6 years
AAA repair at Attendance	6cm 68%	5cm 76%	5.5cm 80%	- 70%
Prevalence of AAA	4% (7.6% in men)	4%	4.9%	7.2%
ODR	12.1%	31.7%	25.3%**	39.6%
Hazard ratio AAA mortality, first publication	0.59 (0.27-1.30), men only	0.31 (0.13-0.79)	0.58 (0.42-0.78)	0.61 (0.33-1.11)
Hazard ratio all-cause mortality, first publication	1.05 (0.92-1.20), men only	-	0.97 (0.93-1.02)	-
Last follow-up	15 years	14 years	13 years	11 years
Last published follow-up	2007	2010	2012	2008
Hazard ratio AAA mortality, last follow-up	0.88 (0.61-1.26)	0.34 (0.20-0.57)	0.57 (0.49-0.66)	-
Hazard ratio all-cause mortality, last follow-up	1.0 (0.90-1.12)	0.98 (0.93-1.03)	0.97 (0.95-0.99)	0.99 (0.94-1.04)
ODR (at last follow-up)	35.5%*	46.0%	42.0%***	-

ODR; Opportunistic Detection and Repair Rate. Ratio of intact AAA repair in control group vs invited screened group; [ $\text{Rate}_{\text{Control}}/\text{Rate}_{\text{Screened}}$ ]. Estimated from tabulated data in publications.

\* Study at this follow-up lacks differentiation between emergency surgery for ruptured and intact AAA

\*\* AAA repair among invited non-attenders assumed based on tabulated data

\*\*\* Rate of repair for symptomatic intact AAAs not stratified for attenders vs. Non-attenders in invited group. Symptomatic repairs thus excluded from calculation.

The condensed results of these trials have been summarized in a Cochrane Review (Cosford 2007), as well as in other meta-analyses, one performed by the United States Preventive Services Taskforce [USPSTF] (Fleming 2005), and additional at mid-term and long-term follow-up (Lindholt 2008, Takagi 2010). All trials have reported outcomes consecutively at various stages of follow-up. The Chichester study has accumulated and published 15 years of follow-up (Ashton 2007), MASS 13 years (Thompson 2012), Viborg 14 years (Lindholt 2010), and Western Australia 11 years follow-up (Lindholt 2008).

The Cochrane meta-analysis in 2007 reported a pooled estimate with an O.R. of 0.60 (95%CI 0.47-078) for death from AAA in the group invited to screening, the corresponding estimate in the USPSTF meta-analysis was 0.53 (95%CI 0.42-0.68). And, in the most recent meta-analysis, pooled data resulted in an O.R. of 0.97 (95%CI 0.95-0.997) for all-cause death among those invited to screening for AAA (Takagi 2012). A similar O.R. of 0.97 (95%CI 0.95-0.99) was reported in the final 13-year follow-up of the MASS study (Thompson 2012).

Thus, in the study populations recruited in the late 1990's an invitation to screening for AAA in elderly men reduced long-term AAA-related mortality by approximately 40%. Also, the invitation to be screened is associated with an approximate 2% reduction in all-cause mortality, possibly by lifestyle changes or subsequent risk factor management in those screened. The decrease in AAA mortality results from prevented ruptures, at the cost of an approximately 2-fold increase in the rate of elective AAA repair.

The results from these trials have served as the basis for the decision to implement today's on-going AAA screening programs, such as the NAAASP in England (Davis 2013), in Sweden (Wanhainen 2011), and in the United States (SAAAVE) .

## Areas lacking information

### Changing epidemiology and AAA management

Between 1995 and 2005 results from 4 large RCTs (Scott 1995, Ashton 2002, Norman 2004, Lindholt 2005) demonstrated that ultrasound based screening for AAA in men 65-74 years of age was an effective method to reduce mortality from AAA-rupture. However, recent data indicate a declining incidence of AAA among men (Norman 2011, Sandiford 2011, Davis 2013). The number of smokers in the population has steadily declined during the past 30 years (Anjum 2012). Mortality from cardiovascular disease has also decreased (Bjorck 2009). Therefore, the target populations in the randomized screening studies may not necessarily be the same as the target populations of today, concerning parameters such as disease occurrence, life-expectancy, and co-morbidity.

Since the 1990's EVAR has steadily increased its proportion of AAA repairs, and is now utilised in over 50% of intact AAA repairs (Levin 2009, Mani 2011). The subsequent lower 30-day mortality of EVAR, and perhaps liberalised indications for treatment, has increased the proportion of individuals eligible for repair and a high rate of surgery in the population has been maintained, especially among elderly (Anjum 2012). At the same time, outcomes after AAA surgery has improved in general (Wanhainen 2008).

Thus, the epidemiological basis used for designing today's implemented screening strategies may have changed considerably.

## Screening Women for AAA

Only one of the randomized studies included a cohort of women (n=3052) of ages 65-80 that were screened for AAA (Scott 2002). The study failed to show any benefit from screening women for AAA. A result commonly used argument against screening women. The study was, however, seriously underpowered. Estimation suggests a power of only 20% to detect a 50% reduction in rupture incidence. Thus, it might not be an effective argument for or against screening of women, and may have contributed to prematurely excluding women from screening programs. Women are underrepresented in studies on vascular disease, despite indications of higher mortality from elective and emergency AAA repair (Hoel 2009). Further epidemiological data on the AAA disease in women is called for, in building a basis for an informed decision on whether to screen women or not (Moll 2011).

## Development of AAAs after a normal screening scan

Although not explicitly assessed in the large RCTs a prevailing and widely implemented model for screening is a one-time examination at 65 years of age (Stather 2013). However, the proportion of men suffering rupture of an AAA before 65, is not insignificant (Swedvasc , Von Allmen 2012). Also, the increasing longevity of the elderly population might result in a longer time-span in which to develop the AAA disease, indicating a possible need for re-screening later in life. Follow-up studies on screened individuals have demonstrated that "new" AAAs can form after a normal scan. Especially, individuals with sub-aneurysmal aortas; aortic diameters in the 25-29mm range, are at increased risk of developing AAAs later in life (Lederle 2000, d'Audiffret 2002, Devaraj 2008, Hafez 2008, Wild 2013). With increased longevity of elderly men and women physically fit at higher ages, newly formed AAAs that earlier never became a clinical issue within the frame of a short lifespan, may become clinically important and cause premature death. The extent and clinical impact of newly forming AAAs and the growth pattern in sub-aneurysmal aortas in a contemporary population are to a large extent unknown.

# Aims

The overall aim of this thesis was to study aspects of AAA screening in a contemporary setting.

The specific aims were:

To determine the prevalence of AAA among 65-year-old Swedish men (Study I)

To analyse risk factors associated with AAA in 65-year-old men (Study I)

To determine the prevalence of AAA among 70-year-old Swedish women (Study II)

To analyse risk factors associated with AAA in 70-year-old women (Study II)

To determine the effect and cost-effectiveness of one-time AAA screening of 65-year-old men in a contemporary setting in a decision analysis model (Study III)

To identify the most important parameters affecting the effect and cost-effectiveness of AAA-screening in a decision analysis model (Study III)

To study the rate of de novo AAA formation in men 5 years following a normal ultrasound scan at age 65-year (Study IV)

To study risk factors for de novo AAA formation in men 5 years following a normal ultrasound scan at age 65-year (Study IV)

To determine the rate of AAA events among 65-year-old men during 5 years following an ultrasound screening examination for AAA (Study IV)

To study the 5-year mortality rate in a cohort of men invited to AAA screening at age 65 years (Study IV)

# Subjects, Material, and Methods

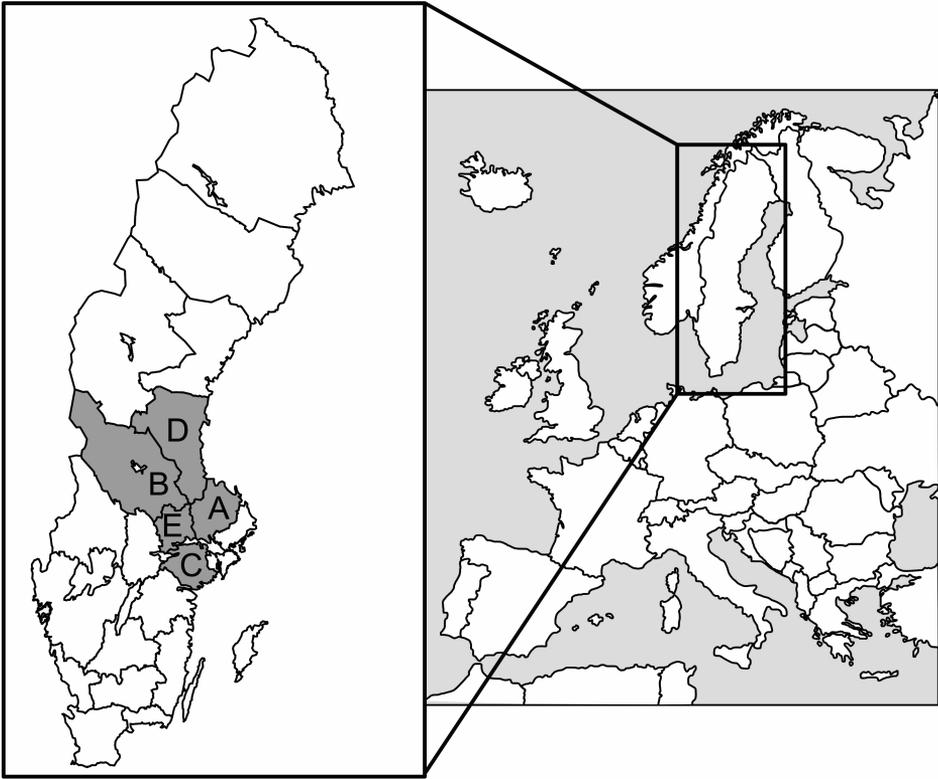
## Subjects, methodology, and study design

### Study I

Following the introduction of a general AAA-screening programme for 65-year old men in the County of Uppsala (A) in 2006, the neighbouring counties of Dalarna (B), Sörmland (C), Gävleborg (D), and Västmanland (E) consecutively launched similar programs in a step-wise fashion, *Figure 1*.

In this multicentre, population-based AAA screening study all 65-year-old men in the five counties were consecutively identified through the National Population Registry, and invited to a one-time ultrasound examination of the infrarenal aorta. Smoking habits, family- and medical history was recorded. Coronary artery disease (CAD) was defined as a history of angina pectoris or myocardial infarction, cerebrovascular disease (CVD) as a history of stroke or TIA, and diabetes mellitus as a history of dietary- or medically treated diabetes.

All 65-year old men with a history of previous AAA-repair and who were alive at the time of invitation to screening were identified in the Swedish Vascular Registry (Swedvasc). From the National Causes of Death Register men in the designated cohort who had died from an AAA before the age of 65 years were identified.



*Figure 1.* The setting of the study. Five Counties in middle Sweden, (A) Uppsala, population 331 898, (B) Dalarna, population 276 454, (C) Sörmland, population 269 053, (D) Gävleborg, population 276 220, and (E) Västmanland, population 251 353, constitute the uptake area. Population figures from 2009.

## Study II

In this dual-centre, population-based AAA screening study, all 70-year-old women (born 1937–1939), identified through the National Population Registry in the two neighbouring counties of Uppsala and Dalarna, were invited during 2007 to 2009 to attend for an ultrasound examination of the abdominal aorta, free of charge. There were no exclusion criteria. The maximum anteroposterior diameter of the infrarenal aorta was measured according to the leading edge to leading edge principle. An AAA was defined as a diameter of at least 30 mm. A set of risk factors equal to that in Study I was recorded.

In addition, all women born between 1937 and 1939 with aortic aneurysm disease (International Classification of Diseases, revision 10, code I.71) as the cause of death before the age of 70 years were identified in the National Causes of Death Registry. Individuals in the designated screening cohort of 70-year-old women, who underwent AAA repair before the age of 70 years,

were identified in the Swedish Vascular Registry (Swedvasc). Women in the cohort under surveillance for a known AAA were identified from local hospital registries.

### ***Comment***

At the time of the study no site-specific codes were used in the registry to record which part of the aorta had ruptured; only the general code I71 was identified. Thus, some deaths may have been due to rupture of the thoracic aorta.

## Study III

In this Markov cohort simulation study, two hypothetical cohorts of 65-year-old men were assigned to either a strategy of invitation to one-time AAA screening with ultrasound (Invited), or a strategy of no screening (Control) where AAA management was based on incidental detection. An AAA was defined as a maximum infrarenal aortic diameter of 30mm or more. The attendance rate was 80% in the invited cohort. The prevalence of AAA was assumed to be the same in the two groups.

### *Model structure*

A Markov model with five exclusive health-states, *Figure 2*, was constructed.

### *Parameters and data sources*

The parameters are summarized in Table 3, and were retrieved from the literature and contemporary original population-based data. The time-dependent probability of an AAA progressing to rupture or elective surgery in the respective cohort was based on the MASS study, which reported in detail on these parameters at 4, 7, 10 and 13 years. (Ashton 2002, Kim 2007, Thompson 2009, Thompson 2012), and corrected for difference in prevalence between MASS and recent Swedish data (Study I). The rate of opportunistic detection of AAAs in the control cohort in MASS at 13 years was estimated at 42% in accordance with a suggested method (Brown 2012).

### *Costs*

All costs are from a perspective of the health service provider. Screening costs were based on actual total costs in on-going screening programmes in Middle Sweden. Cost and effect were discounted at 3.5% annually. The costs are presented in Table 2.

### *Outcome*

Measures of outcome in the model were: effect in life-years (LY) and quality adjusted life-years (QALYs), incremental cost efficiency ratio (ICER) in €

per life-year gained (LYG) and per QALY gained, absolute risk reduction (ARR) for AAA-related death per 10 000 invited, relative risk reduction (RRR) for AAA-related death, and LYG per prevented death from AAA. Results were determined at 10, 13, and 40 (life-time) years of follow-up.

#### Validation

The outcome of the model was validated against the outcomes observed in the MASS study.

Table 2. *Costs in the model*

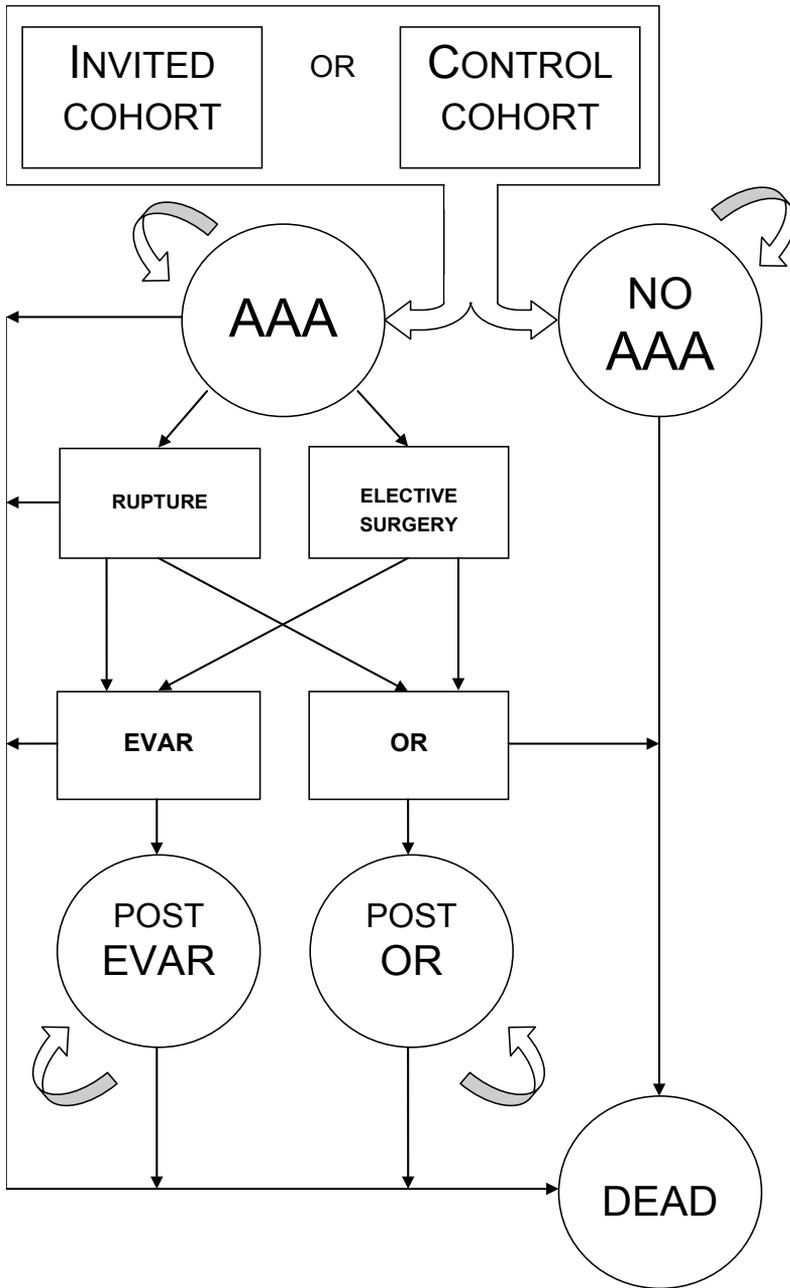
Parameter	€	Range tested	Sources
Invitation	5,39		Actual costs from Swedish screening program
Ultrasound screening exam	16,45	€ 10 to € 40	Actual costs from Swedish screening program, MASS
Surveillance per year	117,80	€ 50 to € 250	Actual costs from Swedish screening program, MASS
Elective Surgery			
OR	30099	x 0.5 to x 2.0	(Mani 2008), (Brown 2012), MASS, (Stroupe 2012)
OR, postop, total per case*	5516		(Mani 2008), (Brown 2012), MASS, (Stroupe 2012)
EVAR	24493	x 0.5 to x 2.0	MASS, (Stroupe 2012)
EVAR, postop, total per case*	5265		(Mani 2008), (Brown 2012), MASS, (Stroupe 2012)
Surgery for rupture (cost x elective surgery)	1.62	1,3-3,0	MASS

OR; open repair, EVAR; endovascular aneurysm repair. All costs have been adjusted to 2012 value.

\* Mean follow-up 5.4 years.

Table 3. *Parameters in the model.*

Parameter	Base case	Range tested in sensitivity analysis	Source
Prevalence, 65-year-old men (%)	1.7	0.1 to 4	Paper I, (NAAASP), (CASS 2001)
Attendance rate	80%		Paper I, MASS
<b>30-day mortality, age-dependent for ages 65-85+:</b>			
OR for intact AAA	1.62%-7.69%		(Swedvasc)
EVAR for intact AAA	0.85%-2.38%		(Swedvasc)
OR for ruptured AAA	17.8%-52.9%		(Swedvasc)
EVAR for ruptured AAA	7.4%-46.2%		(Swedvasc)
Proportion EVAR/OR, repair for intact AAA	50%		(Swedvasc)
Proportion EVAR/OR for repair of ruptured AAA	10%		(Swedvasc)
<b>Time-dependent rates at; 1-4, 5-7, 8-10, 11-13, and 25 years</b>			
Annual risk of surgery for intact AAA in invited cohort	4.89%, 2.75%, 1.81%, 1.38%, 0.00%		MASS, (Swedvasc)
Annual risk of surgery for intact AAA in control cohort	1.46%, 1.56%, 1.02%, 1.46%, 0.00%		MASS, (Swedvasc)
<b>Time-dependent rates at; 1-4, 5-7, 8-10, 11-13, and 30 years</b>			
Annual risk of rupture in invited cohort	1.01%, 1.00%, 1.18%, 1.46%, 0%		MASS
Annual risk of rupture in control cohort	1.97%, 2.29%, 2.33%, 2.03%, 0%		MASS
Probability of surgery in case of rupture, invited	23.69%	up to x2	MASS
Probability of surgery in case of rupture, control	31.17%	up to x2	MASS
Population mortality	Life-tables, ages 65-105		(SCB), (HumanMortalityDatabase)
Relative annual non-AAA related mortality of individual with AAA, and individual post-surgery for rupture	1.11, 1.19	1.0 to 3.0	(Mani 2009), (Duncan 2012), (UKSAT 1998), (Newman 2001), Hultgren[26], (Freiberg 2008)
Relative risk reduction in non-AAA-related mortality in invited group	0.53%		MASS
Opportunistic detection rate in control cohort at 13 years follow-up	42%	25 to 85%	MASS
Utility, 65-69, 70-79, 80+ years	0.83, 0.81, 0.74		(Burstrom 2001)



*Figure 2.* The Markov model. Circles represent health-states and boxes represent events. The thin lines with arrows depict possible pathways for individuals in the model. A curved arrow represents the possibility of an individual remaining in a health-state for consecutive cycles. AAA; Abdominal aortic aneurysm, EVAR; Endovascular aneurysm repair, OR; Open repair.

## Study IV

In this population-based longitudinal cohort study all men identified in the National Population Registry in the County of Uppsala, born 1941 and 1942, were invited to screening for AAA with ultrasonography (US) at age 65 years (primary screening cohort) during the years 2006 and 2007.

The cohort of men born 1941-1942, was re-invited during the years 2011 to 2012 for an US examination of the abdominal aorta at age 70 years. Individuals with a history of AAA repair were excluded from invitation. No other exclusion criteria were used.

Information on smoking habits, family and medical history, as well as current medication was collected at ages 65 and 70 from those attending screening. Smoking status was classified as never, former or current.

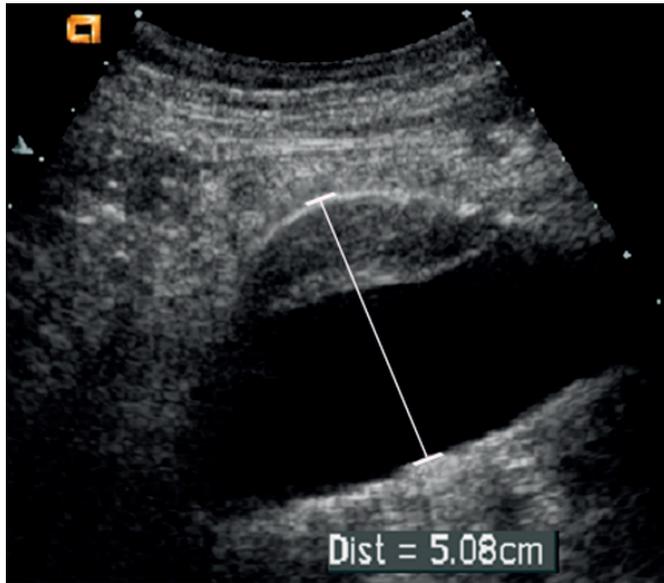
Mortality-data was retrieved from the National Population Registry. Information on AAA-repair of screening detected and opportunistically detected AAAs (detected outside of screening program) was retrieved from the Swedish Vascular Registry (Swedvasc) for the past 5 years.

## Ultrasound

The baseline examination at screening included a single ultrasound scan in which the maximum infrarenal diameter was measured according to the leading edge to leading edge principle (LELE) with the ultrasound transducer longitudinal to the aorta (Singh 1998). With this method the diameter is measured from the leading edge of the near aortic wall to the leading edge of the far aortic wall, in an anterior to posterior plane, *Figure 3*.

Other methods of measuring the maximum infrarenal aortic diameter exist. In UKSAT the maximum diameter was measured from outer wall to outer wall (OTO) in the antero-posterior plane (UKSAT 1998). In the MASS study, it was recorded by measuring inner wall to inner wall (ITI). In the implemented NAASSP in England ITI is used, and a recent study confirming the expected difference of 3mm between the two methods indicated that ITI was more reproducible (Hartshorne 2011). The potential difference in measurements between LELE and the other two methods have not yet been scientifically evaluated.

Ultrasound is deemed accurate to within 5-8mm when measuring the antero-posterior diameter of abdominal aorta, and it has been suggested that this inaccuracy can be brought down to 2-3mm with systematic training (Singh 1998, UKSAT 1998).



*Figure 3.* The maximum anteroposterior infrarenal aortic diameter measured according to the leading edge to leading edge principle. Calipers extend from the leading edge of the near wall to the leading edge of the far wall.

### Definition of an AAA

In all studies in this thesis a maximum infrarenal aortic diameter of 30mm or more was consistently used as the threshold for AAA diagnosis (McGregor 1975, Hirsch 2006, Moll 2011).

### Definition of a sub-aneurysmal aorta

A sub-aneurysmal aorta, sometimes referred to as an “Aneurysm in Formation”, was defined as a maximum infrarenal aortic diameter in the range of 25-29mm (Hafez 2008, Wild 2013).

### Surveillance intervals

According to regional clinical practise, individuals in Studies I,II, and IV, with infra-renal aortic diameters  $\geq 25$ mm were scheduled for US-surveillance at regular intervals; 25-29mm after five years, 30-39mm after 2 years, 40-44mm after one year, 45-49 after 6 months, and  $\geq 50$ mm every three months.

### Threshold for AAA repair

According to regional clinical practise, AAA repair was considered at 55mm or more, or in individuals with symptomatic or rapidly ( $>1.0$ cm/year) expanding AAAs.

## Statistics and Ethics

Statistical evaluation of the data in all four studies was performed with a computer software package (SPSS PC version 19.0-20.0, SPSS, Chicago, IL, USA).

(Paper I+II+IV) The independent samples t-test was used for comparison of continuous data. Proportions are presented with 95% confidence intervals. An uncorrected  $\chi^2$  test was used for comparison of two proportions.

(Paper I+II): A univariable analysis of the variables was made by cross-tabulation of proportions and means stratified by normal or aneurysmal aorta. Associated factors with  $P < 0.10$  in the univariable analysis were entered into a multivariate logistic regression model where odds ratios were calculated and presented with 95% confidence intervals. To avoid statistical interference the different smoking variables were entered separately into the same multivariate regression model. To correct for multiple comparisons significance was assumed when  $P < 0.01$ .

(Paper III): The data analysed was retrieved from literature and from clinical registries reporting data on a population level. The Markov model was developed and implemented with the TreeAge Pro 2012 Healthcare software package (TreeAge Software, Williamstown, MA, USA).

(Paper IV) Risk factors associated with AAA formation with  $P < 0.1$  in a univariable analysis were entered as covariates into a Cox proportional hazards regression model; where hazard ratios (HR) and 95 per cent confidence intervals (95% CI) were calculated.  $P < 0.05$  was considered statistically significant.

Study I, II, and IV were approved by the Ethics Committee of the Uppsala/Örebro region. No ethics approval was necessary for study III.

## Etiological Fraction

In **Study I** the Etiological Fraction (EF) was calculated based on the O.R. of a risk factor associated with AAA in men screened for AAA.

The term attributable fraction encompasses a group of fractional measures with the aim of assessing the impact or contribution of risk factors on the incidence of a disease under exposure (Rothman 2008). There seems to be considerable variation in the semantics of the various fractional measures. Common terms included in this entity are etiologic fraction (EF) and excess fraction. In this study we calculate the attributable fraction/etiologic fraction/excess fraction from the odds ratio of a risk factor, using the “rare disease assumption”. The odds ratio, a descriptive statistic and a measure of effect, describes the strength of association between two binary variables. It is an essential part in logistic regression. Odds refer to the ratio of the number of individuals having an event to the number not having the event. The odds ratio is the ratio of the odds with exposure and that of non-exposure.

The odds ratio is calculated differently than the relative risk, but it asymptotically approaches it for small probabilities “rare disease assumption” (Greenland 1982). Therefore, at low (approximately <0.10) disease occurrences, it can effectively be used to approximate risk and rate ratios (Greenland 1988, Rothman 2008).

Calculation of attributable fraction/etiologic fraction:

The excess caseload due to exposure has been called excess fraction. It can be displayed as  $(A1-A0)/A1$ , where A1 is the number of cases in a hypothetical cohort where all individuals have been exposed, and A0 is the number of cases in the hypothetical cohort when no individuals have been exposed.

R0 (=A0/N) is the incidence proportion with a cohort of N individuals where none has been exposed. R1 (=A1/N) is the corresponding proportion in an equally sized cohort where all individuals have been exposed.

R1/R0 is termed the (causal) risk ratio, sometimes referred to as relative risk.

In a comparison between an exposed group and a control group:

*A relative risk of 1 means there is no difference in risk between the two groups.*

*An RR of < 1 means the disease is less likely to occur in the exposed group than in the control group.*

*An RR of > 1 means the disease is more likely to occur in the exposed group than in the control group*

When a relative risk exceeds 1, reflecting an impact of risk factor exposure on the incidence of the disease, it can be expressed as an excess relative risk. The risk is usually expressed relative to R1. Thus, the excess fraction:

$$(A1-A0/A1) = (A1/N-A0/N)/A1/N = (R1-R0)/R1 = (R1/R0-1)/(R1/R0) = (RR-1)/RR$$

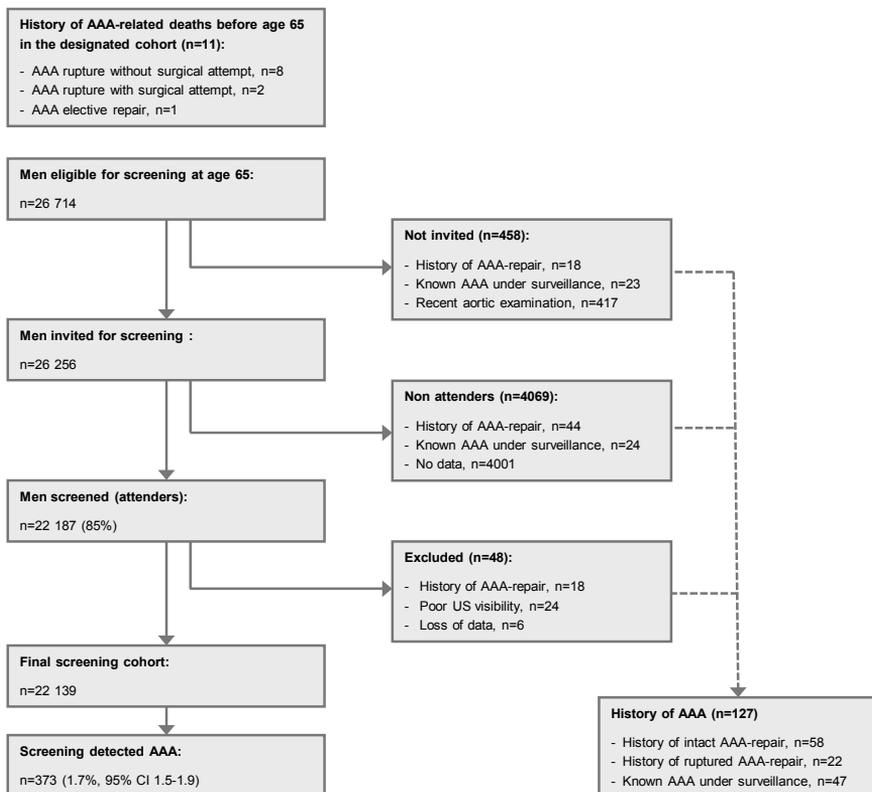
is equal to the relative risk fraction. And under the “rare disease assumption” the O.R. is used as the relative risk estimate, resulting in the EF for a specific risk factor with a specific O.R. being estimated by:

$$EF_{risk\ factor} = \frac{(OR_{risk\ factor} - 1)}{OR_{risk\ factor}}$$

# Results

## Study I

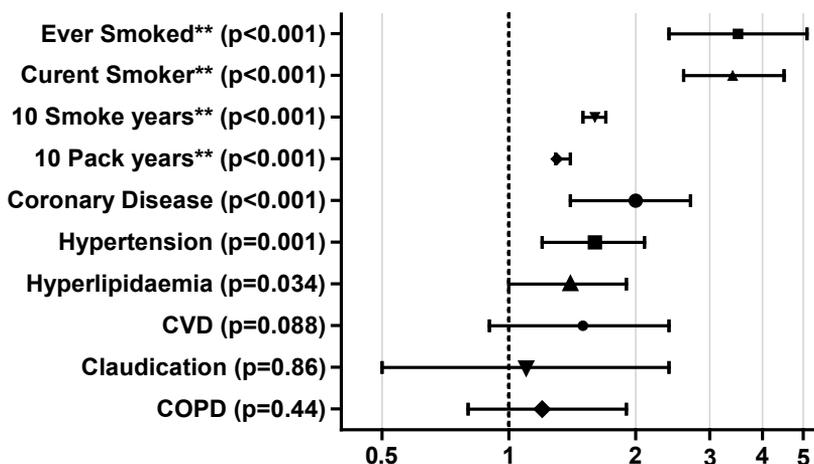
Between 2006 and 2010, 26 256 men were invited to screening, of whom 22 187 accepted (85%, 95% CI 84-85). A total of 80 living 65-year old men had a history of AAA-repair and 47 men were under surveillance for a known AAA. Nine men in the designated cohort were reported to have died from an AAA before the age of 65. Of 14 678 HQs distributed, 14 620 were completed (99.6%). The study profile is displayed in *Figure 4*



*Figure 4.* Trial profile. AAA indicates abdominal aortic aneurysm; US, ultrasound.

Among 22 139 men with a valid ultrasound measurement, 373 AAAs were detected (1.7%, 95% CI 1.5-1.9). The prevalence of previously known AAA (repaired or under surveillance) in the total population eligible for screening was 0.5% (0.4-0.6). Thus, the estimated total prevalence of the disease in the population was 2.2% (2.0-2.4). Seventy per cent of all screening detected AAA were <40 mm. An aortic diameter between 25-29 mm was observed in 395 men (1.8%, 95% CI 1.6-2.0). The mean and median maximum infrarenal aortic diameter were both 19 mm (95% CI 19-19 mm, range 9-88 mm), *Paper (I), Figure 3.*

The risk factor distribution is displayed in *Paper (I), Table 2.* Smoking, CAD, and hypertension were independently associated with AAA in a multivariate logistic regression model, where smoking yielded the highest odds ratios, *Figure 5.* The etiological fraction for smoking was 71%.



*Figure 5.* Multivariable logistic regression analysis of variables\* associated with presence of an AAA. Vertical dotted line represents O.R. of 1, i.e. no risk increase for variable.

\*Variables with  $p < 0.1$  in the univariate analysis were included in the analysis.

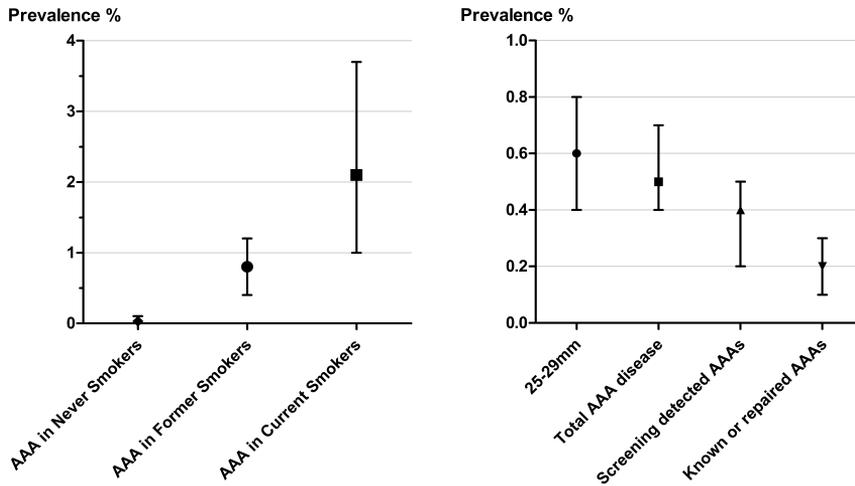
\*\*Smoking variables were entered separately into the same analysis.

## Study II

A total of 6925 70-year-old women were identified, and all were invited for screening. Of these, 12 (0.2%, 95%CI 0.1-0.3) were known to have an AAA, either repaired or under surveillance. Eleven had undergone AAA repair before the age of 70 years and were alive at the time of invitation to screening; seven had elective repair at ages 65–69 years and four had undergone

emergency repair for rupture when aged 62–68 years. Ten of these 11 women had a history of smoking. One woman (with history of smoking) had a known AAA (31 mm) under surveillance. Furthermore, seven women born between 1937 and 1939 had died from aortic aneurysm disease between the age of 60 and 69 years.

A total of 5140 (74.2%, 95%CI 73.2-75.3) accepted the invitation. An infrarenal diameter less than 25 mm was observed in 5091 women (99.0%, 95%CI 98.7-99.3) and a diameter of 25–29 mm in 30 women (0.6%, 95%CI 0.4-0.8). A total of 19 AAAs were detected (0.4%, 95%CI 0.2-0.5). Thus the total prevalence of AAA (known and screen-detected) among 70-year-old women was estimated at 0.5% (95%CI 0.4-0.7). In screened women the mean aortic diameter was 17 (95%CI 16- 17) mm and the median diameter was 16 (range 9–54) mm, *Paper (II), Figure 1a+b*. Of the 19 AAAs detected, 14 were small (below 40 mm); only one exceeded 50 mm (54 mm). Prevalence rates are summarized in, *Figure 6*.



*Figure 6.* Overview of AAA prevalence rates according to smoking status (Left). Prevalence rates for sub-aneurysmal aortas, total AAA disease, screening detected, and known or repaired AAAs (Right). Error bars indicate 95% confidence interval.

Univariable analysis of risk factors associated with AAA among screened women is shown in, *Paper (II), Table 1*. A multivariable analysis identified smoking as the only independent risk factor for AAA, *Table 4*.

Table 4. *Multivariable logistic regression analysis of risk factors associated with abdominal aortic aneurysm in 70-year-old women*

Risk factor	Odds ratio	<i>P</i>
Ever smoked*	20.29 (2.70, 152.65)	0.003
Current smoker*	12.43 (4.91, 31.44)	< 0.001
10 smoking-years*	2.22 (1.58, 3.12)	< 0.001
10 pack-years*	1.70 (1.36, 2.14)	< 0.001
Hypertension	1.58 (0.58, 4.33)	0.369
Hyperlipidaemia	2.34 (0.87, 6.17)	0.086
Claudication	3.97 (0.84, 18.88)	0.083
Renal insufficiency	3.51 (0.40, 30.56)	0.256

\*Each smoking variable was entered separately into the multivariable analysis. Values in parentheses are percentages, with 95 per cent confidence intervals.

## Study III

### Base Case analysis

At 13 years follow-up the ICER (€/QALY gained) was 14706, and 56.5 QALYs were gained by inviting 10 000 65-year-old men to screening. The corresponding ICER using life-years (LY), (€/LY gained) was 11558, and LY gained were 71.9. The absolute risk reduction from death from AAA at 13 years was 15.1/10000 invited; 530 needed to be invited to prevent one death from AAA, and 4.8 years were saved by preventing one death from AAA. By reducing the absolute risk of death from AAA from 0.36% among invited to 0.21% among controls, the relative risk reduction for death from AAA was 42%.

Analysis revealed that a 65-year-old man with an AAA of any size would, on average, extend his life-expectancy (undiscounted) by 1.2 years; from 14.9 years to 16.1 years by taking part in an AAA screening program. The corresponding mean extension of life-expectancy for a man with any AAA fated to expand enough to ultimately generate an AAA event (surgery or rupture) was 2.6 years; from 13.9 to 16.5 years. Also, he would reduce the absolute risk of premature death from rupture from 24% to 14%, and increase the probability of surgery for intact AAA from 18% to 38%, at the price of raising the risk of death from elective surgery from 0.4% to 0.7%.

A summary of the base case analysis, predicted for each length of follow-up, are presented in Table 5.

Table 5. Base case effect and cost-effectiveness according to length of follow-up

	10 years follow-up	13 years follow-up	Life-time follow-up
Effect, Life-years per person, Invited/(Control)	7.9072/(7.9026)	9.5209/(9.5137)	13.1543/(13.1401)
ICER, €/life-year gained in invited cohort	18552	11558	5783
Life-years gained per 10000 invited cohort	46.7	71.9	142.4
Effect, QALYs per person, Invited/(Control)	6.3941/(6.3904)	7.6285/(7.6228)	10.3237/(10.3128)
ICER, €/QALY gained in invited cohort	23265	14706	7570
QALYs gained per 10000 invited cohort	37.3	56.5	108.8
ARR, death from AAA per 10000 invited	13.4	15.1	16.4
NNS to prevent one death from AAA	597	530	488
RRR, death from AAA, %	49.2	42.1	40.2
Life-years gained for each prevented AAA death	3.5	4.8	8.7

ICER; incremental cost-efficiency ratio, QALY; quality adjusted life-year, ARR; absolute risk reduction, NNS; numbers needed to screen. All effects and costs are discounted at 3.5% annually. ARR, NNS, and RRR are unaffected by discounting.

## Validation

The validation procedure resulted in output highly congruent with MASS results, with no significant differences in predicted number of key events in the model cohorts versus the observed key events in MASS at 13 years follow-up.

## Sensitivity analysis

The results of the sensitivity analysis, at 13 years, are presented in, *Paper (III), Table 4*. The parameters with the most influence on cost-effectiveness were the AAA prevalence and the rate of opportunistically detected and repaired AAAs in the control group. In *Figure 7*, the ICER per LYG, and ICER per QALY gained is plotted against the range of prevalence rates tested in the model.

## Comment

The rate of opportunistic detection and repair (ODR) of AAAs in the control group, was one of the two most influential parameters in the cost-effectiveness analysis. Other, than from randomised screening trials this rate is difficult to obtain from scientific literature, and a contemporary estimate of this parameter appears important. The ODR used in the model was based on MASS results at 13-years follow-up. However, prior to implementing the model an estimate of this parameter was obtained by extracting Swedvasc data on rate of AAA repair from a representative county in Middle Sweden with a stable population of 275,000, utilising a single vascular centre that makes few or no referrals of vascular cases. The rate of surgery of intact

AAAs 4 years preceding the screening initiative and 4 years post screening, for 65-year-old men, was compared and resulted in an estimated ODR of 39% at 4 years, slightly higher to the 4-year ODR of MASS of 25%. With screening programs deployed in Middle Sweden mainly around 2008-2009, an estimate of the ODR at a follow-up of more than 4 years is not yet possible.

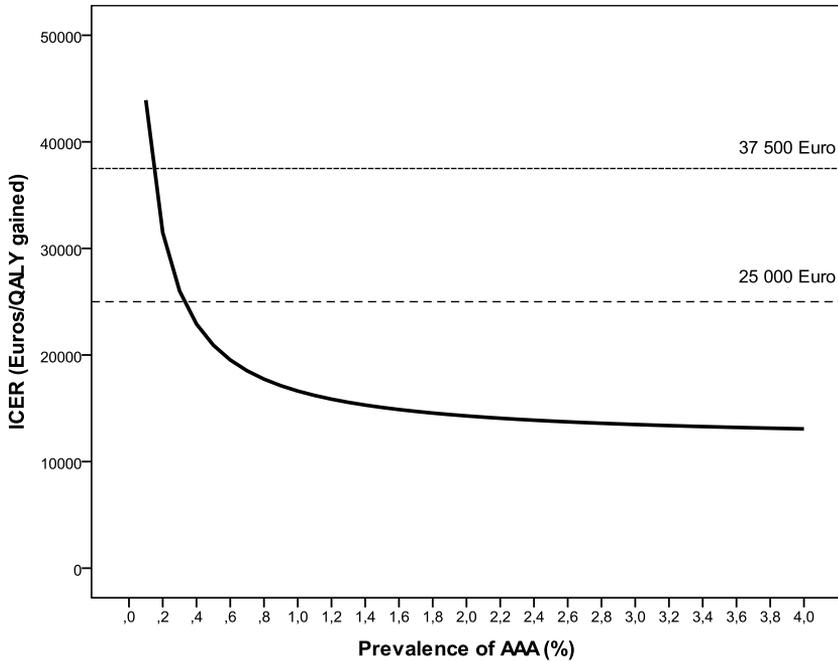


Figure 7. The incremental cost-efficiency ratio (ICER) in € per QALY gained versus the tested range in prevalence. Willingness-to-pay (WTP) thresholds in the figure were based on current NICE values; £20 000/£30 000 per QALY gained (€25 000/€37 500). Follow-up is 13 years. All effects and costs are discounted at 3.5% annually.

# Study IV

## Attendance, prevalence, diameters, deaths, mortality, and AAA repair

In the National Population Registry, 3270 65-year-old men were identified. Two men had a history of AAA repair, one for a ruptured AAA at age 64 and one for intact AAA with unknown date of surgery, and they were not invited and thus excluded from the study. Of the remaining 3268 invited men 2736 (83.7%, 95% CI 82.5-85.0) attended, of whom 2702 (98.8%, 95% CI 98.3-99.2) also completed a health questionnaire. A diameter of less than 25 mm was recorded in 2652 (96.9%, 95% CI 96.3-97.6) and a sub-aneurysmal aorta in 40 (1.5%, 95% CI 1.0-1.9). Forty-four (1.6%, 95% CI 1.1-2.0) had an AAA, of which one had an AAA already under surveillance, and the remaining 43 were screening detected at age 65. The mean infrarenal aortic diameter at age 65 was 18.5 mm (95% CI 18.3-18.6). The trial profile and main outcome are displayed in, *Figure 8*.

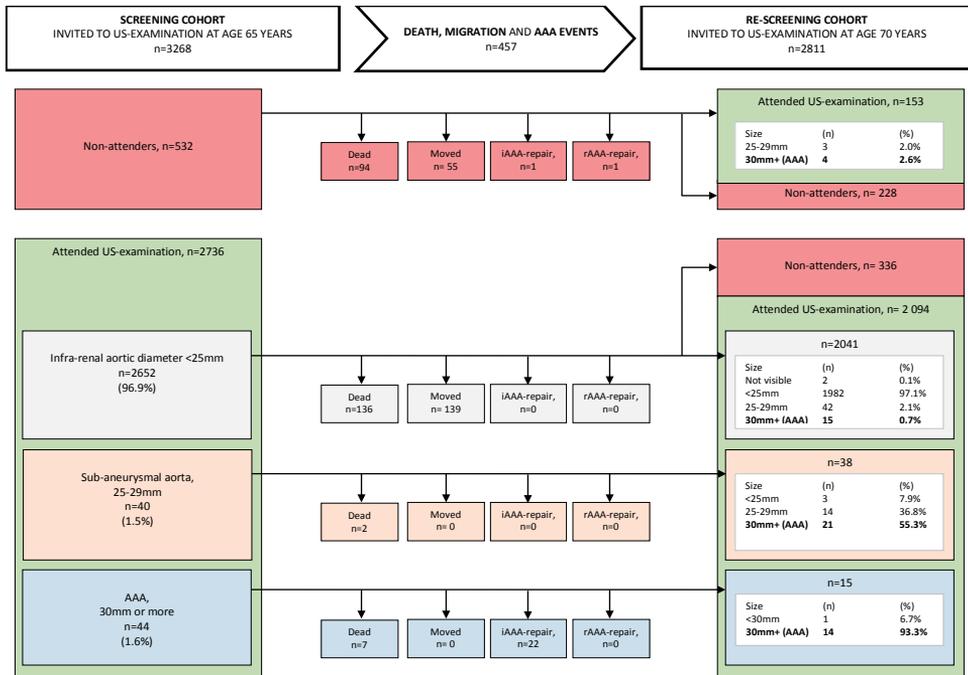
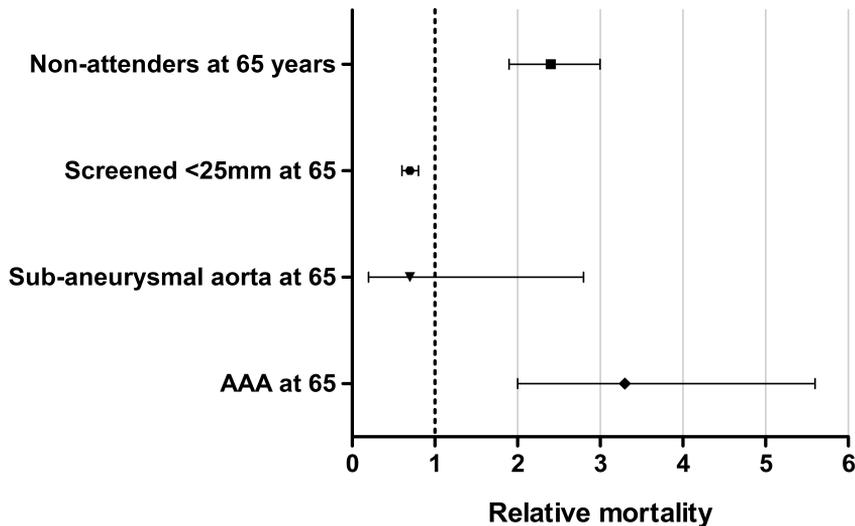


Figure 8. Trial profile and main outcome

After five years, 23 had had elective AAA-repair, of whom 5 subsequently had died of non AAA-related causes, and one had had ruptured AAA repair and died during surgery. In addition, 239 men with a non-aneurysmal aorta were reported dead, and 194 had moved out of the catchment area. Thus, of all men invited at age 65 years 245 had died resulting in a 5-year mortality of 7.5% (95% CI 6.6-8.4). Of the remaining 2811 men re-invited to an US-examination at age 70, 2247 (79.9%, 95% CI 78.5-81.4) attended, of whom 2239 (99.6%, 95% CI 99.4-99.9) also completed a health questionnaire. The total prevalence of AAA at age 70 was 2.4% (95% CI 1.8-3.0), and of sub-aneurysmal aortas 2.6% (95% CI 2.0-3.3). The mean infrarenal aortic diameter at age 70 years was 19.4 mm (95% CI 19.3-19.6), significantly larger than at age 65 ( $p<0001$ ).

The relative 5-year mortality in the respective sub-groups is displayed in *Figure 9*. A total of 22 of 44 (50.0%, 95% CI 34.6-65.4) AAAs detected or known at age 65 completed iAAA repair during the study, resulting in an overall rate of surgery among those attending at age 65; of 22 of 2736 (0.8%, 95% CI 0.5-1.1).

The 5-year events of the men with AAAs stratified by size at age 65 are displayed in, *Figure 10*.



*Figure 9.* The relative mortality in the respective sub-groups. Relative mortality for the entire cohort is 1 (dotted black line). Error bars indicate 95% confidence intervals.

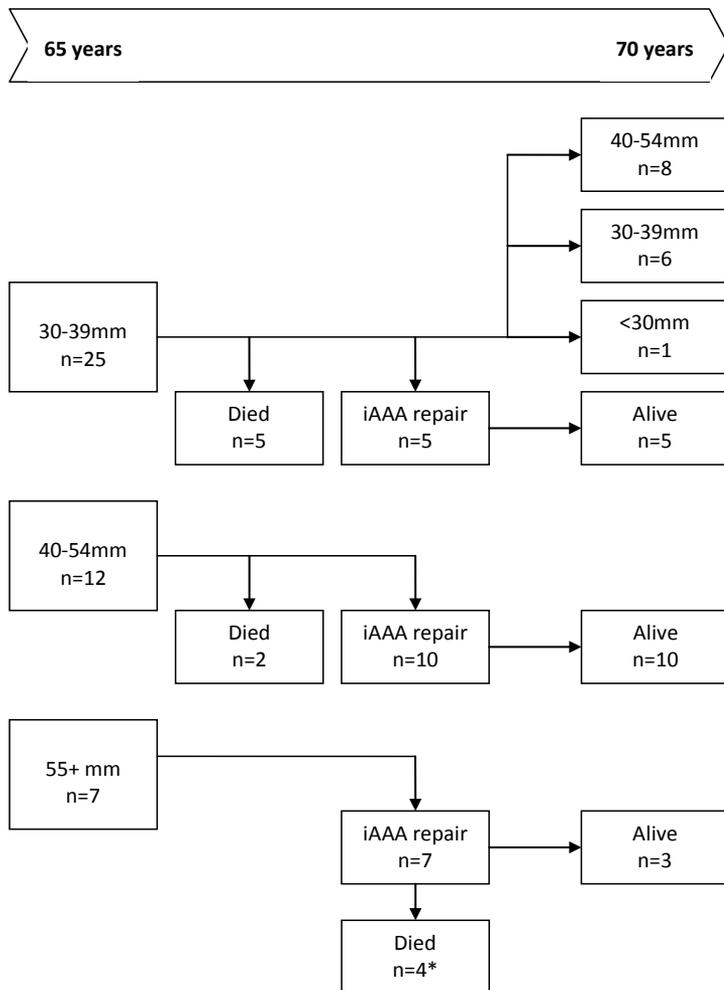


Figure 10. Five-year-events for individuals with a screening-detected AAA or AAA in surveillance at age 65, stratified by size of AAA. \* These patients died after the perioperative period, of non AAA related disease.

### AAA-formation

A total of 2059 men with an aortic diameter of less than 30mm at age 65 and complete data on risk factors were included in a risk factor analysis for AAA formation. In the univariable analysis; stratifying those not expanding to an AAA (n=2023) versus those that did develop AAAs (n=36) after 5 years; resulted in a sub-aneurysmal aorta at age 65, current smoking, and claudication displaying association ( $p < 0.05$ ) with the risk of expansion to an AAA, Paper (IV), Table 1.

In a subsequent multivariable regression analysis, including risk factors with  $p < 0.10$  in the univariable analysis, the infrarenal aortic diameter at age 65 or a sub-aneurysmal aorta at age 65, and current smoking were the only independent risk factors for expansion to an AAA within 5 years, Table 6.

With a surveillance threshold of 25mm at the age of 65, 21 of 36 (58.3%, 95% CI 40.8-74.5) individuals developing AAAs after 5 years would have been identified. There was no difference in size of the AAAs at age 70 comparing those who had had an aortic diameter below 25 mm with those who had an sub-aneurysmal aorta at the age of 65, median size 32 and 33 mm, respectively.

Table 6. *Cox proportional hazards multivariable regression analysis of risk factors associated with the risk of expanding to an AAA within 5 years in men screened normal at 65 years.*

Risk Factor	HR	95% CI	<i>p</i>
Current smoker	2.78	(1.38-5.57)	<b>0.004*</b>
Sub-aneurysmal aorta at 65-years ‡	59.78	(29.87-119.63)	<b>&lt;0.0001*</b>
Infrarenal aortic diameter at 65 years (mm)‡	1.66	(1.53-1.82)	<b>&lt;0.0001*</b>
Coronary Disease	1.44	(0.58-3.57)	0.433
Claudication	0.59	(0.12-2.95)	0.525

Hazard Ratio; HR.

‡ Diameter-related variables were entered separately one at a time into the model. Values of non-diameter-related hazard ratios are presented from analysis together with variable “Sub-aneurysmal aorta at 65-years”.

\* Independent, significant risk factors.

# General Discussion

In an effort to study aspects of screening for AAA in a contemporary setting, we performed two cross-sectional multi-centre population-based studies of one-time screening of 65-year-old men, and 70-year-old women in Middle Sweden. (Paper I and II).

In combination with contemporary results from other population-based studies, results from our screening study of 65-year-old men were applied in a decision-analysis model to evaluate today's effect and cost-effectiveness of one-time screening of 65-year-old men (Paper III). Effort was also put into identifying the key parameters affecting the cost-effectiveness of one-time screening. Furthermore, to determine outcomes in a cohort of men screened at age 65 years, we performed a prospective longitudinal cohort study with 5-year follow-up of men invited to screening at age 65, where mortality, AAA events, and AAA formation were studied (Paper IV).

The findings in this thesis coincide with recently emerging results from other reports indicating a changing epidemiology of the AAA disease. The change in the epidemiology of the disease and concurrent changes in AAA management may have implications on the fundamental conditions for AAA screening of elderly men and women. The findings in this thesis will be interpreted, and an approach at putting them into a contemporary perspective regarding AAA screening is made in the following sub-sections of this discussion.

## Changing Epidemiology

### Prevalence and risk factors

Merely one or two decades ago, concordant reports presented signs of a continuous increase in AAA incidence and prevalence (Melton 1984, Bengtsson 1992, Acosta 2006). In the USA, the largest screening study ever reported prevalence rates of 4-5% among over 120,000 screened predominately male subjects (Lederle 2000). Between 1995 and 2004 large randomized population-based screening trials demonstrated AAA prevalence rates of 4-7% in men 65 and older, Table 1. Also, the study by Lederle, together with others, unanimously confirmed the strong association between smoking and AAA (Newman 2001, Singh 2001).

In **Study I** the observed prevalence of screening detected AAA of 1.7% in 65-year-old men was lower than expected. In comparison, the prevalence in 65-year-old men in a comparative study of the 4 randomised screening trials (CASS 2001) was 3.5% to 4.5%, twice that in **Study I**. In the ADAM screening program from 1992 to 1997, the mean age was 66 years with a prevalence of 4.2%. Lastly, in a Swedish necropsy study encompassing the years 1958 to 1986 the prevalence of AAA among 65-year-old men approximately 30 years ago was extrapolated to 3.5% (Bengtsson 1992). However, the latest report (2011-2012) from the largest nationwide AAA screening programme (NAAASP) indicates a prevalence of 1.5% in 65-year-old men. Other reports from the UK, New Zealand, and Australia similarly indicate a marked reduction in AAA incidence since around half a decade before the year 2000 (Norman 2011, Sandiford 2011, Anjum 2012).

Chronologically, falling rates of smoking in both men and women in western societies coincide with the observed reduction in incidence. In *Figure 11*, the proportion of daily smokers among men and women in Sweden are displayed. The falling rates since 30 years are evident for men of all age groups, whereas for older women the pattern deviates somewhat with fairly constant rates. In (study I) the odds ratio for AAA among ever smokers was 3.5. Consequently, the Etiological Fraction (EF) of smoking, the excess cases attributable to the specified risk factor, was 71% in **Study I**, similar to the EF (75%) observed for smoking by Lederle et al (Lederle 2000).

Assuming the same EF on the 3.5% (95% CI, 3.0 to 4.0) prevalence of AAA among 65-year-old men in the 1958 to 1986 Swedish necropsy study indicates that 2.5% ( $0.71 \times 3.5\%$ ) could be explained mainly by smoking and the remainder 1.0% by other factors. The smoking rate in men today is one third of that in the 1980's, *Figure 11*. Applying the contemporary frequency of current smoking to the 1958 to 1986 Swedish necropsy cohort would result in a total prevalence of 1.8% (one third of 2.5% + 1.0%), approximately the same prevalence found in this study.

A similar indication of smoking as an important cause of the reduction in AAA disease is demonstrated by Anjum et. al. using the IMPACT model (Anjum 2012). In conjunction with the publication of **Study I**, this link between the temporal pattern of smoking and the pattern of AAA disease was also speculated on by Lederle where smoking rates in the USA steadily increased, to peak in the 1980's, where after they have steadily declined to one third today (Lederle 2011).

Today's changing smoking habits may therefore largely explain the lower-than-expected prevalence of AAA in the present report, and a further

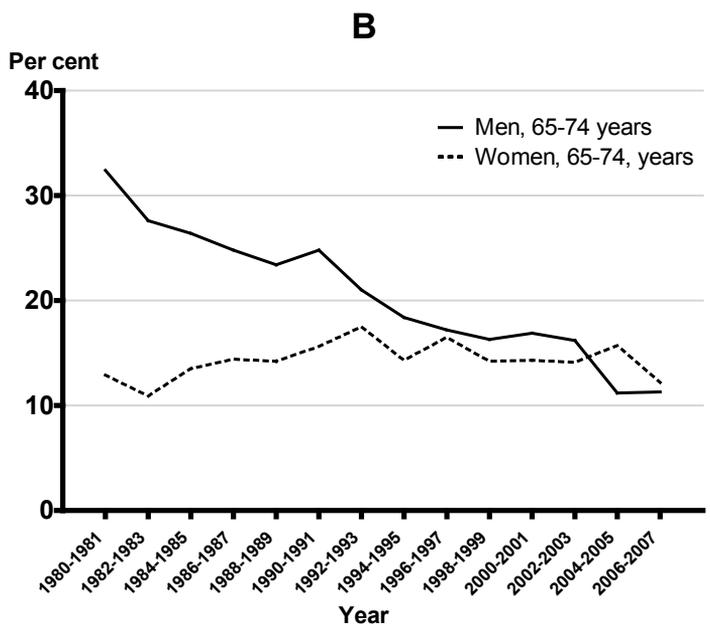
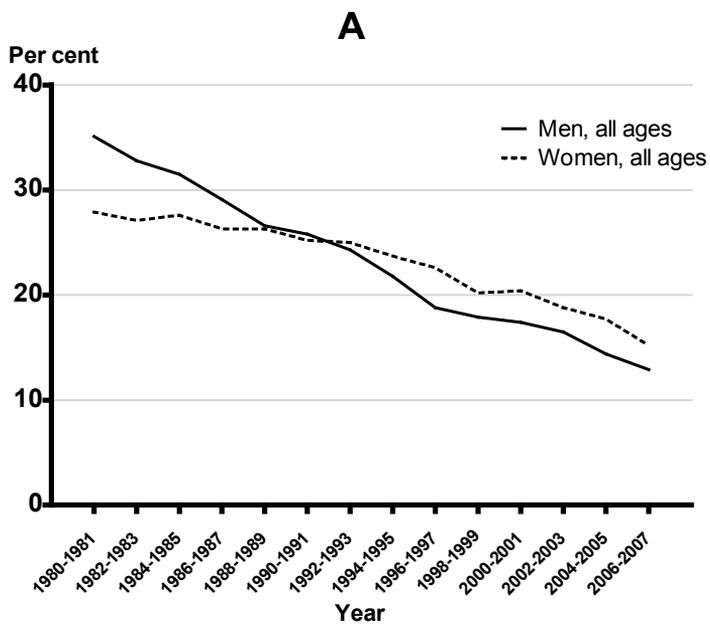


Figure 11. Proportion of population with daily smoking in Sweden, 1980 to 2007, stratified by gender (A) and by gender for age groups 65-74 (B). Source: Statistics Sweden.

decline in prevalence could be expected over time as the rate of daily smoking among men continues to drop in Sweden.

Further implication that today's populations differ from those in the screening trials in the late 1990's is gained when studying the change in longevity in elderly over time. Over the past decades, the average life expectancy of a 65-year-old man in Sweden has increased significantly, from 14 years in 1975 to 18 years in 2009 (SCB). The improved longevity may be caused by various factors such as differences in exposure to known risk factors. This suggests that the current target population differs from the populations examined in previous investigations of AAA prevalence among 65-year-old men, often dating 10 to 30 years back. In the ADAM cohort (Lederle 2000), the reported rate of ever smokers among men was 75% compared with 64% in the present report, and similar differences exist for other risk factors such as hypertension rates of 54% versus 37% and coronary artery disease rates of 37% versus 11%. In Sweden as a whole, coronary artery disease mortality rates decreased by 53% in men between 1986 and 2002 (Bjorck 2009).

### Rate of AAA repair

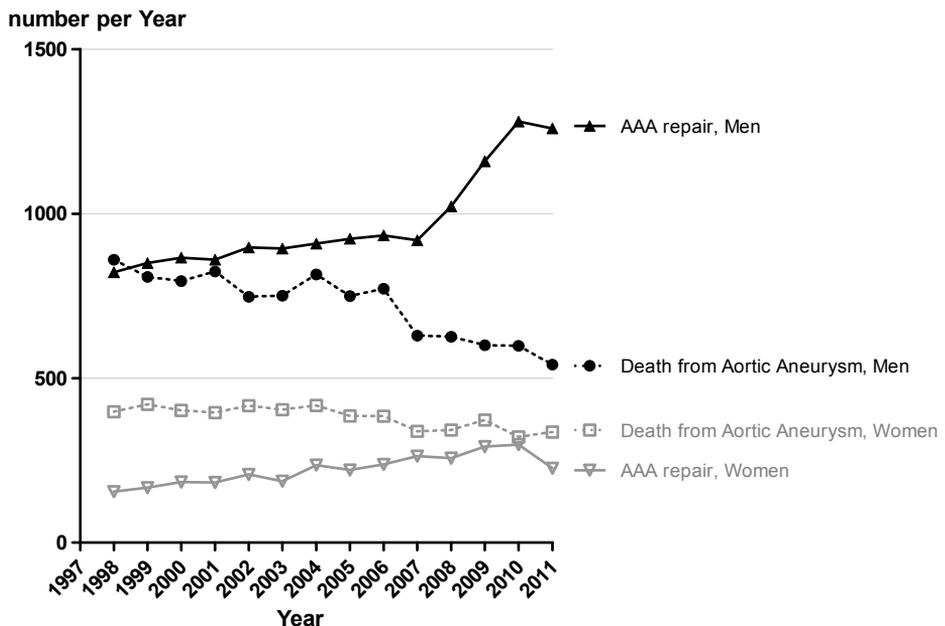
In **Study I**, the average annual number of screening detected AAAs was 133, whereas the current average annual number of AAA repairs in men  $\geq 65$  years of age in the catchment area was 177. With about one third of screening-detected AAAs eventually undergoing repair (Ashton 2007) and only a small number of AAAs detected before screening, it is difficult to explain the current workload. The number of AAAs requiring surgery among non-attenders is unlikely to explain this observed discrepancy. Thus, a significant proportion of today's caseload must emanate from other sources. There are a number of conceivable explanations, and they are not necessarily mutually exclusive.

A conceivable explanation may be the development of new clinically relevant AAAs after 65 years of age. An altered risk factor exposure may result in a delayed presentation of the disease among genetically predisposed individuals. The longer life expectancy also results in a longer lifespan at risk to develop the disease. An alternative explanation may be an overall rapid decrease of the disease in the population. Although, there are no signs of a decrease in AAA repair workload in Sweden (Swedvasc), this may be an effect of the natural course of the disease with a delay in surgical presentation. The current surgical workload may thus originate from a historical cohort with a higher prevalence of AAA than seen today, a so-called cohort phenomenon.

A contributing explanation may also be a shift in the pattern of AAA repair where a slight steady increase in elective AAA repair has been observed in the UK from the late 1990's, coinciding with a sharp decline in mortality

from ruptured AAA (Anjum 2012). A similar observation was reported in Sweden for the years 1994 to 2010 (Mani 2013). In both studies a shift in AAA repair to older individuals was observed, as well as a strong increase in the use of EVAR. This trend appears evident also when accessing the national in-hospital registry and extracting the annual crude number of AAA repairs performed between 1997 and 2011 in Sweden, *Figure 12*. In the same figure the crude number of deaths attributable to aortic aneurysm for men and women are plotted. Clearly, a marked drop in deaths caused by aortic aneurysm is visible, and this trend was unchanged if rates were calculated per 100,000 individuals.

According to these mortality statistics the proportion of deaths attributable to aortic aneurysm has declined from 1.8% to 1.2% of all deaths for men between 1997 and 2011, and from 0.9% to 0.7% for women, respectively.



*Figure 12.* Annual crude number of AAA repairs in the in-hospital registry in Sweden stratified by gender. Also, the crude annual number of deaths attributable to aortic aneurysm, stratified by gender. Source: Open-Access Statistics Database, Swedish National Board of Health and Welfare.

In the study from the UK, a proportion of the decrease in AAA mortality was attributed to the increase in elective AAA repair. A similar effect in Sweden cannot of course be ruled out. Possible explanations for the increased elective repair may be a higher degree of incidental detection of AAAs, since the increase in elective repair and decline in mortality appeared before the wide

introduction of AAA screening programs, in combination with more individuals eligible for AAA repair.

The current epidemiology of AAA appears to be in a dynamic phase, with a complex pattern of coinciding effects which has changed the setting for AAA management dramatically. Undoubtedly, the established population-based screening programmes will continue to deliver further data on the contemporary AAA epidemiology, necessary for future decision making.

### Implications for screening (effect and cost-effectiveness)

On the basis of results from the four randomized controlled trials, screening elderly men with ultrasound for abdominal aortic aneurysm (AAA) has emerged as an evidence-based way of reducing mortality from ruptured AAA. Although no trial has assessed the optimum age for AAA screening, current recommendations generally consist of a one-time ultrasound examination at 65 years of age (Stather 2013).

The observed changes in the epidemiology of AAA disease highlight the need to re-evaluate different screening strategies on the basis of modern epidemiological data, which may influence the design of the screening programs.

In **Study III** we aimed to evaluate the effect and cost-effectiveness of the most widely adopted screening model; one-time screening for AAA in 65-year-old men, within a setting of contemporary epidemiology. Using a Markov model; a strategy of screening versus a strategy of no screening was analysed, *Figure 2*. The base case ICER at 13-years follow-up, the follow-up time equivalent to the longest follow-up available in MASS, was €14706/QALY gained in the invited cohort. This was well below the commonly referenced WTP threshold of €25000 (£20000) of UK's National Institute for Health and Clinical Excellence (NICE). According to a guidelines for cancer treatment publication 2007 from the National Board of Health and Welfare in Sweden, an incremental cost efficiency ratio (ICER) of less than €11 680/QALY gained was deemed low, €11 681 – €58 411 medium, €58 412 – €116 822 high, and more than €116 822 very high. Thus, one-time screening of 65-year-old men was cost-effective in a context of contemporary AAA epidemiology and management.

In the sensitivity analysis, the prevalence of AAA and the rate of opportunistic detection and repair were the most important parameters affecting the impact and cost-effectiveness of AAA screening.

Effort was put into priming the model with input parameters from comprehensive, contemporary validated population-based registries and recent original population-based data, to reflect modern AAA epidemiology. In some models, the AAA event rates are based on average annual expansion rates for AAAs, but these may be based on heterogeneous, sometimes small cohorts of individuals with small AAAs or large AAAs in individuals unfit

for surgery. For purposes of simplicity, and to avoid possible multiplication of small errors in applied expansion rates, we opted to extract the crude time-dependent AAA event rate for an AAA in the invited and control group, from the largest and most influential screening RCT, MASS (Thompson 2012).

### **Prevalence**

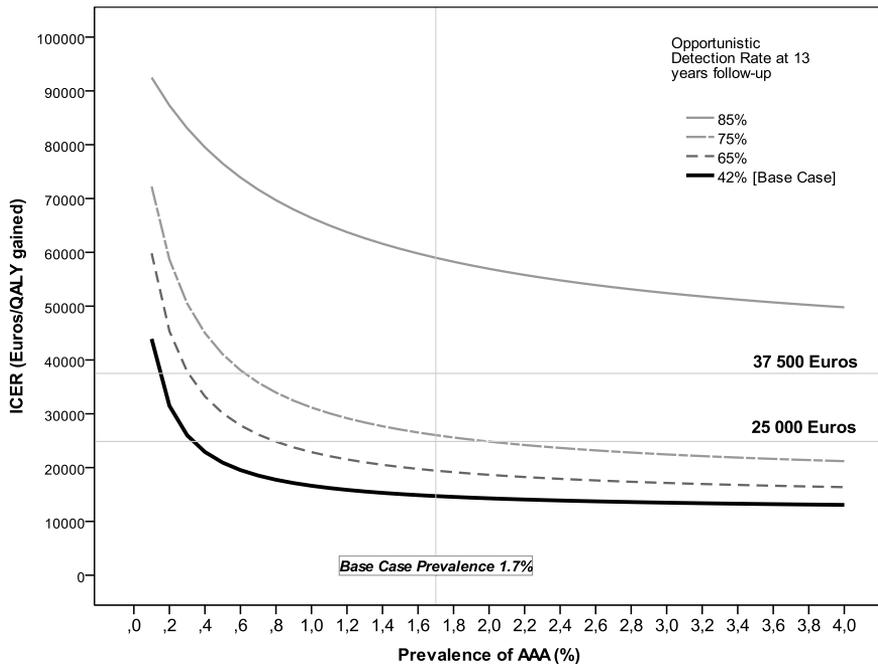
In the sensitivity analysis the cost-efficiency of AAA screening was fairly insensitive to prevalence of AAA down to approximately 0.5%, *Figure 13*. From the sensitivity analysis it was also evident, as expected, that the ARR and QALYs gained per 10 000 invited decreased in proportion with falling prevalence rates. Also, at low prevalence rates few individuals per 10 000 invited can benefit from gained life-years, and the cost of the entire screening system is carried by a few individuals resulting in dramatically higher ICERs per QALY or life-year gained, Table 5. A falling prevalence may also indicate a need for exploration of targeted screening in men, using instruments to select risk groups with high prevalence to maintain a clinically reasonably high absolute risk reduction per 10 000 invited as well as improved cost-efficiency.

### **Opportunistic Detection and Repair of AAAs**

The rate of opportunistic detection and repair of AAAs in the control group signals how often AAAs are incidentally detected by other methods than ultrasound screening. Commonly this means finding an AAA incidentally on a CT or MRI scan performed for some other ailment. With increasing use of CT (Brenner 2007) in diagnostics of abdominal pain and in the emergency department, the rate of opportunistic detection can be expected to rise. Logically, if a large proportion of AAAs is already detected before screening the cost-efficiency of ultrasound screening will decrease, as the prevalence of undetected AAA among those ultimately attending screening will be reduced.

At 4 and 13 years follow-up in MASS, the opportunistic detection and repair rate (ODR) in the control group was 25% and 42% of that in the group that attended screening, respectively. This was also the base case ODR used in the model. However, there are data suggesting a possibly higher ODR today. In **Study I** 29% of the total AAAs identified, were known or repaired. The corresponding figure for MASS was 11% (Ashton 2002). In addition, using Swedvasc, an estimate of the 4-year rate of intact AAA surgery in the population predating screening versus the rate post screening indicated a 39% rate of opportunistic detection and repair for 65-year-olds; higher than in MASS, but equal to that in the Western Australia RCT at 4 years, Table 1. In MASS and the Viborg trial, where inclusion stopped right before year 2000, the ODR at 4 years increased with longer follow-up, with approximately 50% after an additional 10 years. Speculating, this would put the

Swedish estimate at approximately 60% at 13-years follow-up. In the sensitivity analysis, *Figure 13*, this would generate an ICER of approximately €20000, still below the threshold of cost-effectiveness according to NICE.



*Figure 13.* The incremental cost-efficiency ratio (ICER) in Euros per QALY gained versus Prevalence of AAA, at different rates of opportunistic detection in the control cohort. Willingness-to-pay (WTP) thresholds in the figure were based on current NICE values; £20 000/£30 000 per QALY gained (€25000/€37500). Follow-up is 13 years. All effects and costs are discounted at 3.5% annually. WTP threshold indicated by horizontal grey lines. Base case prevalence by perpendicular grey line.

Two of the limitations in the model, might however affect the final cost-effectiveness result in today's setting. Firstly, results from **Study IV**, signalling a higher repair rate of screening detected AAAs than in previous reports, together with multiple reports of increased elective AAA repair in the population, could imply that the intact AAA repair rate in the model, which is based on MASS data, is an underestimate. This effect would be most prominent in the screened group with a higher elective rate of repair. Consequently, if a generally increased intact AAA repair rate in the population causes a reduction in AAA rupture mortality (Anjum 2012), the risk reduction gained from screening, and hence the cost as well as the efficiency, may be slightly underestimated in our model. An increased intact AAA repair rate is, however, difficult to simulate within the constraints of our model. Secondly, in MASS the size distribution of the detected AAAs leaned towards somewhat

larger AAAs than detected in **Study I**, which could imply that the general risk of AAA events over time in a contemporary setting is reduced to some degree countering the effects of a generally increased repair rate.

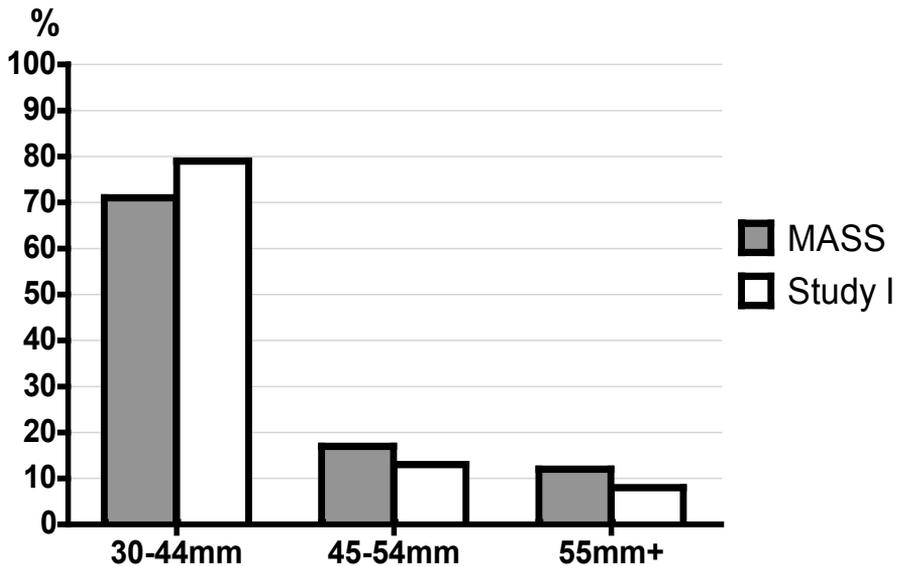


Figure 14. AAA size distribution in MASS vs (Study I).

### Future screening

Paradoxically, the subsequent implementation of nationwide AAA screening programmes in Europe (Earnshaw 2011, Wanhainen 2011), and USA (Lederle 2011) has coincided with significant changes in the epidemiology and management of AAA observed in the last decade, all potentially fundamental conditions for the rationality of AAA screening. The profound changes in AAA management and epidemiology are easily illustrated when key parameters at 10 years follow-up in today's epidemiology are tabulated with those in the MASS study, Table 7.

The current dynamics of AAA epidemiology is also reflected in other recent decision-analysis of AAA screening cost-efficiency. And, from the variations in the magnitude of the resulting ICERs, it can be assumed that models are based on very different assumptions of risks and costs. Recently published model studies from the UK, Norway/Netherlands, and Denmark reporting cost-effectiveness of one-time screening of 65-years-old men have employed base case prevalence rates of 3.3% to 8.9% (Kim 2007, Spronk 2011, Sogaard 2012). These rates may reflect international variations in AAA occurrence, but may also be historical overestimates in view of large

scale accumulating data from the UK NHS screening programme reporting rates of 1.5% (NAAASP). The Dutch/Norwegian study report base case ARR rates 5-6 times higher than those in this study, but comparable ICERs in €/life-year gained in the long-term, €4 340/€9 860, compared to €5 783 in this study. The Danish study reported the lowest base case ICER in €/QALY gained of €685, which decreased to €437 in a sensitivity analysis with reduced prevalence (1.63%) and reduced AAA growth rates.

Table 7. Changes in key AAA parameters and cross-referencing of 10-year model data with 10-year cost-effectiveness data from MASS (Thompson 2009). Life-years and costs are discounted at 3.5% annually.

<b>Parameter</b>	<b>Model</b>	<b>MASS</b>
Age/Strategy	65, one-time	65-74, one-time
Follow-up	10 years	10 years
Mean age at time of screening	65 years	69.2 years
General life-expectancy of a 65-year-old man	18.51 *	15.19 **
Prevalence of AAA in 65-year-old men	1.7%	3.5%‡
Proportion EVAR	50%	12.8%
30day-mortality, OR for intact AAA	reference	x 1.92
Non-AAA-related, relative risk reduction in mortality in invited cohort†	0,53%	0,53%
ARR for death from AAA per 10 000 invited	13.4	41.6
NNS to prevent one death from AAA	597	192
RRR, death from AAA	49%	48%
Life-years gained with invitation to screening per 10 000 invited	46.7	131.5
Life-years gained for each prevented death from AAA	3.5	3.2
Incremental Cost Efficiency Ratio (€/life-year gained), Invited vs. Control	18 552	10 139

EVAR; Endovascular Aneurysm Repair, AAA; Abdominal Aortic Aneurysm, ARR; absolute risk reduction, NNS; numbers needed to screen, RRR; relative risk reduction.

\* Based on population statistics from Sweden 2012. \*\* Based on population statistics from UK in 1998, estimated midpoint of inclusion in MASS. ‡ Data from Collaborative Aneurysm Screening Study Group, 2001. †Non-AAA related relative risk reduction in mortality calculated from 13-year data in MASS.

The comprehensive model of one-time screening of 65-year-old men from the UK, employing patient-level AAA-event data from MASS at 4 years and a 3.5% annual discounting, predicted an ICER of €4789 /QALY gained at 30 years follow-up, and we assume the study used a 3.5% AAA prevalence in 65-year-old men, comparing to our of €5783 at life-time follow-up. Based on data from 2002, the same study predicted an ICER at 10 years follow-up (2009) of €11200/life-years gained, almost exactly the figure (€10 139), Table 7, that was observed in a cost-efficiency analysis using actual costs from MASS (Thompson 2009) at 10 years follow-up, thus demonstrating a remarkably precise and dependable prediction model.

At present, one-time screening of 65-year-old men appears cost-effective, and in comparison with other established disease screening programs delivering ARR of disease specific death of 7-20 per 10000 invited (Hewitson 2008, Nelson 2009, Schroder 2009, Atkin 2010, Gotzsche 2011), the 15 per 10000 ARR of AAA screening in this study, in combination with an estimated 8.7 years saved per prevented rupture, seems clinically relevant. Suspecting that additional large scale multicentre screening RCTs are unlikely, further input on the natural history of screening detected AAAs from recently implemented screening programs is essential for model-based evaluation and optimisation of contemporary screening strategies.

## Screening Women for AAA

The only randomised screening trial including women, the Chichester AAA screening program, invited 15775 subjects, of which 59% were women. In that report, where no difference in mortality from rupture was observed between women screened and not screened, the authors concluded that screening women was neither clinically indicated nor economically viable (Scott 2002). However, the low total number of ruptures in the trial may have rendered it underpowered to detect an effect of screening. With lack of evidence, the role of screening women for AAA remains unclear.

We performed a dual-centre cross-sectional population-based ultrasound screening study of 70-year-old women and determined prevalence and associated risk factors, and supplemented with validated registry data on AAA repair and mortality (Study II). The prevalence of screen-detected AAA in **Study II** was 0.4%, the lowest reported among population-based studies in predominantly white populations, representing a quarter of the prevalence among 65-year old men (Study I) and one sixth of that among 70-year-old men (Study IV) recently studied in the same geographical area. This confirms the gender ratio of approximately 1:4-6 found in previous studies (Lederle 2001, Derubertis 2007), indicating a possible reduction in prevalence similar to that reported for men (Study I) (Conway 2012). A reduction was also implied when comparing the prevalence of AAA among 70-year-old women with that found in a Swedish necropsy study (Bengtsson 1992) reporting a rate of 1.2% for the same age group.

Similar to the results in **Study I** among the 70-year-old women a profile with generally lower rates of coronary disease, hypertension, and hypercholesterolemia was observed compared to previous studies (Lederle 2001, Derubertis 2007). As observed in men (Study I), this implies a decrease in exposure to risk factors during the past decades.

Smoking was the only independent risk factor for AAA in **Study II**, and the association was very strong with 95% of women with AAA reporting active smoking or a history of smoking. The stronger association with smok-

ing is also apparent in *Figure 15*, displaying the prevalence of AAA among men and women in **Study I+II**, stratified by smoking status. The prevalence among actively smoking women (2.1%) exceeds the overall prevalence in men, as well as formerly smoking men, while displaying a very low rate (0.03%) among women who do not smoke. This distribution of aneurysms to almost exclusively smoking women effectively rules out general population-based screening of women. A similar falling trend in daily smoking is evident for women, *Figure 11*, although elderly women seem to have maintained a level and fairly low rate of smoking compared to younger women. With the strong link to smoking, it is reasonable to assume that reduced smoking rates in women can account for the apparent reduction in AAA prevalence in women, similar to that observed in men.

Women with AAA present and receive treatment for AAA later in life than men with AAA (Bengtsson 1993, Lederle 2008, Lo 2013, Starr 2013). However, in **Study II** approximately 1/3 of the AAAs identified had been repaired before age 70, a third of them for rupture at ages 62-68. In addition seven women had died from ruptured AAA at ages 60-69. This finding has implications for the threshold age in a potential screening program for women, which might have to start at the same age as in men to be effective. Although 90% of the repaired women were smokers, additional indicators to identify which women are at risk of early AAA disease could prove essential in designing a targeted screening program to prevent early rupture in women.

Targeted screening of women in risk groups has been advocated (Kent 2004, Derubertis 2007) and this is mainly based on observed high prevalence rates among smoking women or women displaying multiple risk factors. Additional arguments are; the discrepancy of women seemingly suffering almost one third to half of all annual deaths from aortic aneurysm, while presenting with only a fourth of the disease prevalence compared to men (Vouyouka 2007), *Figure 12*. With significant changes in AAA epidemiology and longevity, apparent among women as well as among men, and reports of higher 30-day mortality rates in AAA repair (Lederle 2008) in combination with 4 times increased rupture rates (Brown 1999) compared to men, the role of screening in women is complex and difficult to ascertain. Further studies evaluating targeted screening strategies for women are warranted.

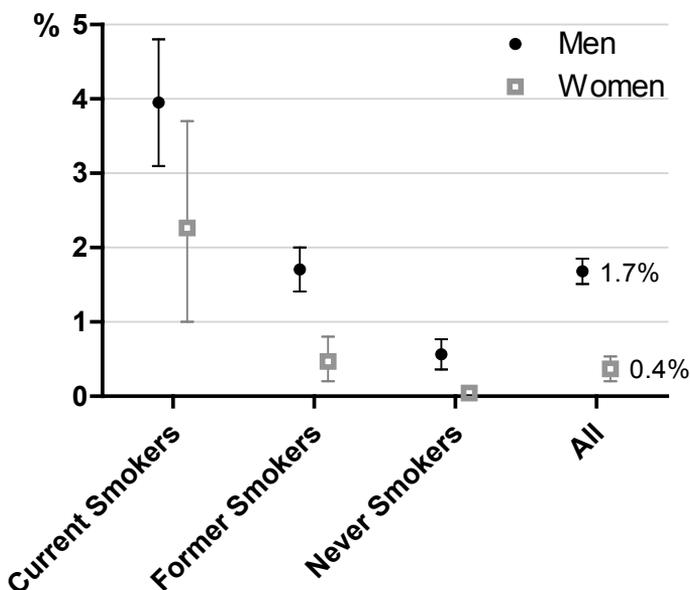


Figure 15. Prevalence of screening detected AAA among 65-year-old men in (Study I) and 70-year-old women (Study II) stratified by smoking status.

## Outcomes in men screened for AAA

The most wide-spread AAA screening strategy; one-time screening of men at age 65, is partially or fully implemented in several countries (Stather 2013). This specific strategy is, however, not evidence-based and several aspects need further research; such as the threshold diameter for surveillance, the long-term natural course of those screened normal as well as the fate of those not attending the screening programme.

In an effort to determine the rate of de novo AAA formation and associated risk factors after a normal scan, the rate of AAA events, and mortality we performed a population-based longitudinal cohort study of men screened at age 65, and re-invited to ultrasound examination at age 70 (Study IV).

### Non-attenders

In **Study IV** the cohort of men comprised part of the larger multi-centre cohort invited in **Study I**, and 16% declined screening at age 65, similar to that in **Study I** (15%). A number of studies describe a reduced health among non-attenders in screening programs (Janzon 1986, Jensen 1996, Ogren 1996), and subjects declining screening in the Chichester, and MASS trial had higher all-cause mortality (Scott 1995, Ashton 2002). This finding was

also evident among non-attenders in **Study IV**, displaying a 2-3 times higher 5-year mortality compared to the entire cohort. However, a third of those alive at age 70 ultimately attended re-screening, and presented with a similar AAA prevalence rate as those examined at both age 65 and 70. Apart from higher rates of smoking, the risk factor profiles were similar to the rest of the cohort. It is possible that they comprise a group of individuals not declining screening due to health related reasons. This finding would then suggest effort should be spent on increasing attendance in this specific group.

### Men screened <25mm at age 65

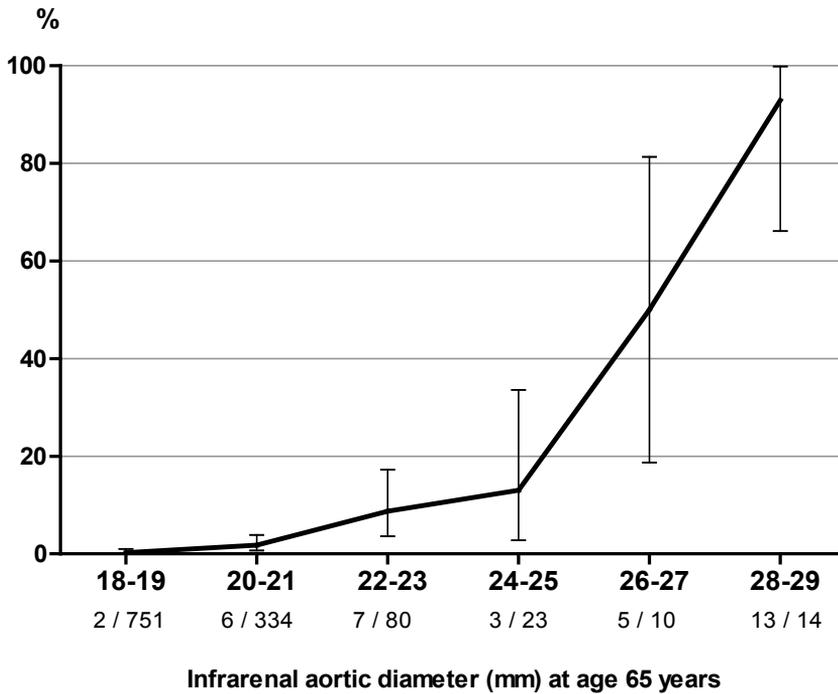
Of men with an initial scan less than 25mm, very few require AAA repair or suffer from AAA related mortality even at long-term follow-up (Darwood 2012), and all-cause mortality seems lower in this group compared to those with sub-aneurysmal or aneurysmal disease (Duncan 2012). This was also observed in **Study IV** with a significantly lower 5-year mortality in men with <25mm aortas at age 65. *Figure 9*. In a study by Emerton et al (Emerton 1994) 223 men with <26mm aortas were re-screened after 5 years, and 1% had developed AAAs, similar to 0.7% in **Study IV**. All AAAs were small. Hafez et al (Hafez 2008) reported that the mean time was significantly longer from screening to AAA event among men with <25mm versus those with 25-29mm. In a twenty-year review of the Gloucestershire program (Darwood 2012) the incidental detection of AAAs after a scan <25mm was merely 0.19%. However, a low, but detectable, risk of AAA events was demonstrated at 0.16% after long-term follow-up, with 0.08% risk of AAA related death. Clearly, this group suffers a negligible risk of AAA events at 5 years following a scan at age 65.

### Sub-aneurysmal aortas and surveillance

The threshold diameter for enrolling an individual in surveillance after an aortic scan is debated. Some reports recommend surveillance in aortas 30mm or more (Scott 2001, Couto 2002), while others support a surveillance regimen in sub-aneurysmal aortas (25mm or more) (Lindholt 2000, d'Audiffret 2002, McCarthy 2003, Devaraj 2008, Hafez 2008, Wild 2013). In a multi-centre observational study with up to 19 years follow-up on outcomes of screening detected sub-aneurysmal aortas, combining data from some of the above referenced reports, 59.6% of sub-aneurysmal aortas progressed to true AAAs (30mm+) after a mean time of 4.7 years, and 8.3% developed AAAs >54mm after a mean time of 13.2 years. The corresponding figure in **Study IV** was 52.5% after 5 years. Although the literature reports only a 1-2% crude risk for a sub-aneurysmal aorta to ultimately generate an AAA event or reach >54mm, with increasing longevity this clinical observation may change and need further evaluation. In **Study IV** no one exceeded 54mm

after 5 years so far reaffirming the screening program's 5-year surveillance interval for this group. The prevalence of sub-aneurysmal aortas in **Study IV**, 1.5%, was similar to that in **Study I**, 1.8%, and proportionally lower among 70-year-old women (Study II) at 0.6%. This is similar to the 2.1% rate in men in the UK screening program (Wild 2013). Due to few observed cases the relative mortality in this group had a wide confidence interval and a meaningful evaluation on mortality was not possible, *Figure 9*. However, other reports have indicated an increased mortality in this group (Freiberg 2008, Duncan 2012), not unlike that of men with AAA.

Studies re-examining men with normal aortas after various time periods have identified sub-aneurysmal aortas as predictors of AAA formation after a normal ultrasound scan (Devaraj 2008, Hafez 2008), and in a sub-set of the ADAM trial subjects with AAA formation after a normal scan had larger initial diameters at the initial scan (Lederle 2000). Smoking has also been identified as a predictor for AAA formation and increased AAA expansion rate (Lederle 2000, Brady 2004, Sweeting 2012), as well as diabetes displaying a protective effect. All men scanned <30mm at age 65 in **Study IV** with complete health-data (n=2059) were included in a risk factor analysis for AAA formation. In a multivariable Cox proportional hazards regression analysis the infrarenal aortic diameter at 65 and current smoking were independent risk factors for AAA formation after 5 years. The increasing risk of AAA formation at increasing diameters is clearly evident, when studying the proportion of individuals that progress to an AAA from a normal aorta according to initial size at screening, *Figure 16*. In **Study IV** no one with an aortic diameter less than 18mm developed an AAA after 5 years. The clearly dominant risk factor was a sub-aneurysmal aorta at age 65 which increased the risk of AAA formation 60-fold, more than 20 times higher than the risk attributed to smoking, Table 6.



*Figure 16.* The observed proportion of individuals with AAA formation within 5 years, according to diameter at screening at age 65 years. Error bars indicate 95% confidence intervals. Exact proportions are displayed below each diameter category.

In **Study IV**, the majority (58%) of de novo AAAs after 5 years were identified with a surveillance threshold of 25mm, which indicated re-scanning after 5 years of the men with 25-29mm at age 65; constituting merely 1.5% (n=40) of all men examined at age 65. In contrast, to identify the remaining 42% of de novo AAAs, all men with diameters of 18-24mm would have had to be enrolled in surveillance and re-examined after 5 years; constituting an additional 56% (n=1535) of all men screened at 65. To numerically identify as many of the de novo AAAs as possible by re-scanning as few as possible, the proportion of individuals with a specific diameter can be plotted together with the proportion of individuals forming AAAs at a specific diameter, *Figure 17*. From this figure, it can be assumed that this surveillance threshold-diameter would be approximately 21mm, where 80% of the de novo AAAs would be identified by re-scanning approximately 15% (n=400) of the cohort screened <30mm at age 65. This would markedly increase the number of individuals needing re-scanning, compared to the present threshold of 25mm, and further highlights the need for more sophisticated methods of selecting which aortas that expands to AAAs and who do not. Thompson et al (Thompson 2010) postulated that only half of small AAAs eventually

expand, and that growth rates can be used to predict the natural history of AAAs. Devaraj et al (Devaraj 2008) speculated on the possibility of using the growth rate of the first four years of surveillance as a predictor of which AAAs became clinically relevant further on, and which AAAs might be left without surveillance. Whether this method can be used to further refine the prediction which sub-aneurysmal aortas that ultimately progress to AAA events is of course unclear, but will be possible to analyse as the cohort study increases in numbers and length of observation.

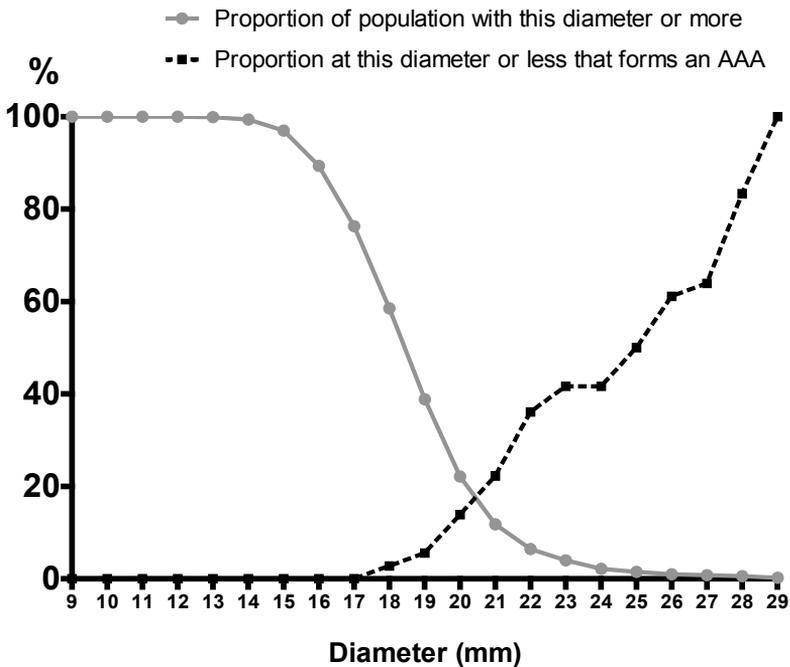


Figure 17. The proportion of the cohort in (Study IV) with the specified diameter or more (grey line). And, the proportion of individuals at the specified diameter or less that forms an AAA after 5 years (dotted line).

Although cost-efficiency of the 25mm-threshold at first glance would appear reasonable; the unclear balance of increased longevity in elderly versus the observed higher all-cause mortality in this group indicates a need for further long-term study of these cohorts to determine the risk of progressing to clinically relevant AAA disease in a contemporary context. In the absence of firm contemporary data on disease progression for this group in a time of changing epidemiology, it would seem reasonable to include men with aortic diameters of 25mm or more at the age of 65 in a continued surveillance programme.

## Men with AAA

Most AAAs detected at screening at age 65 are small. Roughly 75% are 3-3.9 cm in size at detection, and the annual rupture rate in these is negligible, and regular ultrasound surveillance is appropriate (Rescan-Collaborators 2013). Large AAAs (>54mm) carry a significant annual risk of rupture and referral for consideration of surgery is warranted (Moll 2011). After the publication of two randomised controlled trials ADAM and UKSAT (Lederle 2002, 2002) comparing immediate surgery with ultrasound surveillance of AAAs in the range 4-5.4cm, demonstrating that long-term survival was not improved by immediate elective repair, the optimal management of these AAAs are periodic ultrasound surveillance as well. The lower perioperative mortality of EVAR (Prinssen 2004, Schermerhorn 2008, Lederle 2009, Greenhalgh 2010) prompted two studies, PIVOTAL and CAESAR, to evaluate the strategy of surveillance versus immediate EVAR for intermediate sized AAAs, however no mortality benefit was demonstrated, and these trials have not altered the optimal strategy of surveillance for AAAs in the range 4-5.4cm (Ouriel 2010, Cao 2011). Still, there is no universal consensus concerning the appropriate surveillance intervals (Moll 2011), and considerable international variation exists (Stather 2013).

In **Study IV** a somewhat lower proportion (57%), *Figure 10*, of AAAs of 3-3.9cm size was found than in **Study I** (70%). Further input from incremental cohorts in the study will determine if this is a singularity or not in **Study IV** due to few total cases, which for now seems the most likely explanation. This may also in part explain the high 5-year repair rate of 50% in **Study IV**, but a contemporary higher eligibility for AAA repair might also contribute to this finding. Although, MASS and the Viborg Screening trial presented 5-year repair rates of approximately 25%, a degree of circumspection when comparing is called for as these trials included men 65-74 years of age with subsequently lower expected fitness for surgery. Comparing with the Gloucestershire screening program (Darwood 2012) enrolling 65-year-old men, approximately similar rates of surgery for 30-39mm AAAs were found, but the 5-year rate (83%) in **Study IV** for 40-54mm AAAs exceeded the 10-year-rate (66%) observed in Gloucestershire.

The only source of documented rupture in **Study IV** occurred among non-attenders at 65. Whether additional ruptures occurred not leading to surgery could not be determined as access to reliable data on causes of death was not readily available for individuals other than those in surveillance, and was a limitation of the study at this point.

With no ruptures among men with screening detected AAAs in addition to no peri-operative mortality despite high rate of surgery, taking part in the first five years of the screening programme appeared safe. All deaths, including those occurring after AAA repair, were from non-AAA related causes in this group. This fact, together with a relative high all-cause mortality in this

group of 3.3, *Figure 9*, confirms observations of non-AAA related causes of death dominating among individuals with AAA (Newman 2001, Freiberg 2008).

## Future perspective

In summary; although one-time screening for AAA was still cost-effective within a contemporary context, the lower than expected prevalence of AAA among 65-year-old men, an unchanged repair rate, and improved longevity of the elderly population, indicate that several issues need to be addressed; most importantly; the threshold diameter for follow-up, the current rate of opportunistic detection of AAA in the population, re-screening of the entire population at a higher age, and targeted screening of smokers.

In addition; screening 70-year-old women who do not smoke is likely to be futile, thus ruling out population screening of women for AAA. Targeted screening of smoking women warrants further evaluation.

# Conclusions

At 1.7%, the prevalence of screening detected AAA among 65-year-old men in Middle Sweden was lower than expected. An additional 0.5% of known AAA disease was observed at age 65 years, constituted of previously repaired AAAs and AAAs under surveillance.

Smoking was the altogether dominant risk factor associated with AAA among screened 65-year-old men, where a history of smoking or active smoking raised the risk of AAA among 65-year-old men approximately 3-fold. Coronary disease, Hypertension, and Hyperlipidaemia contributed to a lesser degree to increased risk of AAA.

The decline in AAA prevalence appeared to be linked to a proportionate decline in rate of smoking among elderly men during the past 30 years.

At 0.4%, the prevalence of screening detected AAA among 70-year-old Swedish women was low, compared to previous reports in western societies.

Smoking was strongly associated with AAA in 70-year-old women, where active smoking increased the risk of AAA by 20 times, and 95% of women with AAA had a history of smoking.

Screening 70-year-old women who do not smoke is likely to be futile, thus ruling out population screening of women for AAA.

In a context of modern AAA epidemiology and management, one-time AAA screening of 65-year-old men appears to be a cost-efficient and an effective health-care intervention.

Important factors affecting the effect and cost-effectiveness of AAA screening are the prevalence of AAA in the population, and the rate of opportunistic detection and repair of AAA in the population.

In men screened normal (<30mm) at age 65, AAA formation after 5 years occurred among 1.3%.

In men screened normal at age 65, increased aortic size at age 65 increased the risk of AAA formation after 5 years, especially among men with sub-aneurysmal aortas (25-29mm), indicating a possible need for surveillance of this group. To a lesser degree, smoking also increased the risk of AAA formation.

A high 5-year rate of repair of screening detected AAAs was observed among men with screening detected AAAs at age 65.

Relative to the entire cohort invited to screening, the 5-year all-cause mortality among men with screening detected AAAs, as well as among non-attenders at age 65, was high.

With documented AAA rupture occurring only among men not attending AAA screening, and no observed peri-operative mortality among individuals with elective AAA repair; the results of the first five years of AAA screening in a cohort of 65-year-old men indicate that the programme is safe.

Although one-time screening for AAA was still cost-effective within a contemporary context, the lower than expected prevalence of AAA among 65-year-old men, an unchanged repair rate, and improved longevity of the elderly population, indicate that several issues need to be addressed; most importantly; the threshold diameter for follow-up, the current rate of opportunistic detection of AAA in the population, re-screening of the entire population at a higher age, and targeted screening of smokers.

## Summary in Swedish

Abdominellt aortaaneurysm (AAA) är en sjuklig, permanent vidgning (bråck) av stora kroppspulsådern i buken (buk-aorta). Ett AAA anses föreligga om buk-aortas vanliga diameter på ca: 20mm är ökad till 30mm eller mer. Den exakta orsaken till att ett AAA uppkommer är inte känd, men flera faktorer ökar risken att utveckla ett AAA; manligt kön, stigande ålder, rökning, ärftlighet och någon eller några av riskfaktorerna för hjärt-kärlsjukdom. AAA är mycket ovanligt före 60 års ålder. Det naturliga förloppet för ett AAA är att långsamt öka i vidd, i genomsnitt 2mm per år, men vid större diametrar tilltar tillväxthastigheten, liksom om individen röker.

AAA är en företrädesvis symptomfri sjukdom, men det vanligaste - och likaledes katastrofala symptomet - är bristning (ruptur). Den årliga risken för ruptur ökar med stigande diameter, och är liten upp till ca: 50-55mm, varefter den snabbt tilltar och kan nå över 30% vid diametrar över 70mm. Ruptur innebär en plötslig, massiv inre blödning där den försvagade kärlväggen i ett AAA brister spontant. Tillståndet är livshotande, och är förenat med totalt sett 80% dödlighet. Merparten av drabbade dör omedelbart utan att nå till sjukhus, och av de som når sjukhus och kan opereras är dödligheten ändå ungefär 50%. En akutoperation för att reparera ett rupturerat AAA är en svår och resurskrävande operation med osäker utgång och med efterföljande intensivvård och ibland svåra komplikationer.

AAA upptäckts vanligen vid undersökning av buken av en läkare eller vid en röntgenundersökning för något annat tillstånd. Upptäckta AAA är oftast små, och följs då med regelbundna ultraljudskontroller tills de eventuellt når 55mm varvid förebyggande kirurgi rekommenderas. Modern, planerad förebyggande kirurgi har, i motsats till operation för ruptur, en total dödlighet på ca: 1-2%. Ett AAA repareras traditionellt med en öppen bukoperation där aorta ersätts med en syntetisk kärilprotes, eller i lämpliga fall med inläggning av kärilprotesen via punktioner i ljumskarna utan öppen bukoperation.

Pga. ett AAAs längre symptomfria stadium och den höga dödligheten vid operation, samt positiva resultat från flera större internationella vetenskapliga studier erbjuds idag omkring 90% av svenska 65-åriga män ultraljudsbaserad screening för AAA i syfte att uppnå tidig upptäckt och möjlighet till förebyggande operation i lugnt skede. Vetenskapliga rapporter i slutet av 1990-talet och början av 2000-talet har påtalat en succesivt tilltagande förekomst av AAA i befolkningen.

## **Delarbete I**

I detta delarbete genomfördes en populations-baserad, multi-center screening-studie där 26256 65-åriga män i Mellansverige inbjöds till en ultraljudsundersökning av buk-aorta och samtidig registrering av riskfaktorer. En betydligt lägre förekomst av AAA än förväntat påvisades, och den starka kopplingen till rökning som riskfaktor bekräftades. Den minskade rökningen i befolkningen sedan 30 år tillbaka bedömdes vara huvudorsak till den låga sjukdomsförekomsten i kombination med en allmänt minskad förekomst i befolkningen av riskfaktor för hjärt-kärlsjukdom.

## **Delarbete II**

Screening av kvinnor för AAA anses vanligen inte motiverat, pga. lägre sjukdomsförekomst och insjuknande i högre ålder med hög risk vid operation. Sjukdomen är dock bristfälligt studerad hos kvinnor, och kvinnor kan för tidigt ha uteslutits från screening-programmen för AAA.

I detta delarbete inbjöds 5140 70-åriga kvinnor i Uppsala och Dalarnas län till en kostnadsfri ultraljudsundersökning av buk-aorta och information om riskfaktorer inhämtades samtidigt. Förekomsten av AAA var mycket låg och kopplingen till rökning starkare än hos män. Nittio-fem procent av kvinnorna med upptäckta AAA rökte eller hade rökt. Baserat på resultaten bedömdes allmän screening av kvinnor inte vara motiverat. Selektiv screening av rökande kvinnor behöver utvärderas ytterligare.

## **Delarbete III**

Minskad förekomst av AAA och samtidigt förbättrad hälsa i befolkningen samt och förbättrade resultat vid operationer kan ha ändrat grundförutsättningarna för screening som infördes baserat på vetenskapliga studier med mycket högre uppmätt sjukdomsförekomst.

I en modell-baserad matematisk simulering utvärderades effekten och kostnads-effektiviteten av screening för AAA bland 65-åriga män. Screening uppnådde en fortsatt god kostnads-effektivitet inom ramen för modern sjukdomsförekomst och kirurgiska resultat.

## **Delarbete IV**

I detta delarbete inbjöds män som inbjöds till screening vid 65 års ålder till en ny ultraljudsundersökning efter 5 år vid 70 års ålder. Nybildning av AAA bland de som screenats normala vid 65 års ålder förekom vid 70 års ålder, ffa. bland rökande män och män som hade en buk-aortadiameter strax under gränsen för ett AAA vid 65. Fler män med AAA genomgick operation inom 5 år än vad som rapporterats tidigare, och en relativt hög andel av männen med AAA avled av orsaker inte relaterade till AAA pga. ökad sjuklighet.

## **Sammanfattning**

Baserat på den observerade minskade exponeringen för riskfaktorer, en lägre än förväntad förekomst av AAA bland 65-åriga män, och en fortsatt hög operationsfrekvens i befolkningen samt ökad livslängd bland äldre; är slutsatsen att den nuvarande screening-modellen kan ifrågasättas. En utvärdering av alternativa modeller är nödvändig. Viktiga frågor att utreda är diameter-tröskelvärdet för ultraljuds-övervakning av buk-aorta, och det eventuella behovet av om-screening vid högre åldrar samt selektiv screening av rökare.

Baserat på resultaten från studien av screenade 70-åriga kvinnor; är vår slutsats att allmän populations-baserad screening av kvinnor för AAA är uteslutet, och att selektiv screening av rökande kvinnor behöver utvärderas.

# Acknowledgements

I wish to express my sincerest gratitude and appreciation to my outstanding tutor, colleague, and friend, associate professor **Anders Wanhainen**, for infallible round-the-clock encouragement and enthusiasm, a heartfelt and including personality, a razor-sharp intellect, and for being a truly exceptional contemporary vascular surgeon.

and to professor **Martin Björck**, my co-tutor, and head of the vascular research team at Uppsala University, for excellent tutorship, never failing warm support, true zeal, and for being a virtual ambulatory ocean of scientific knowledge.

*I would also like to express my sincere appreciation to the following people who have been directly involved in, or contributed to the research projects of this thesis:*

My co-authors of the papers in the thesis; **Kevin Mani**, **Mikael Gürtelschmid**, **Khatereh Djavani-Gidlund**, **Anders Hellberg**, and **Jonas Lundkvist**, all exceptionally talented individuals, skilled scientists and contributing with invaluable data, as well as encouraging, brilliant, and constructive criticism in all the work to finally piece the papers together. I can't wait to continue with further inspiring scientific co-operation.

**Ewa Pihl**, screening coordinator and co-worker in Dalarna, for being an extraordinary professional, for never failing energy and joy, and for single-handedly scanning and small-talking over 15000 men and women in the heartland of Sweden in the name of science and saving lives.

**Staffan Nilsson**, former head of the Centre for Clinical Research (CKF) in Dalarna, and **Marianne Omne-Pontén**, former director of CKF, for maintaining a superb platform for clinical scientists in Dalarna.

The vascular research nurses at the vascular laboratory, Akademiska Sjukhuset, Uppsala; **Linda Lyttkens**, **Sofia Lindell**, **Katarina Bruun**, and **Nilla Westöö**, for delivering high-grade research data with tremendous speed. **Marie-Louise Jonsson**, ultrasound technician in Uppsala for helping out in

Dalarna, and all **ultrasound technicians** at the vascular laboratory in Uppsala, and the screening centres in Gävle, Eskilstuna, and Västerås

**Thomas Troëng**, vascular surgeon, for delivering invaluable Swedvasc-data enhancing our studies.

**Leena Johansson**, secretary at the department of surgery in Uppsala, for literally thousands of completed, data-base registrations.

**All members of the vascular surgery research team in Uppsala**, for striving scientifically and clinically, and providing a pleasant debate-climate at all our meetings.

*I would also like to express my sincere appreciation to the following:*

My team-leader, **Bo Westman**, Teflon-coated and always joyous, for magnificent, twenty-four-seven encouragement during my training in vascular surgery, and for being one of the most outstanding vascular surgeons I have ever encountered. And, to his wife, **Ann-Christine**, for sharing him so nobly.

My dear fellow vascular surgeons on the vascular surgery team at the department of surgery in Falun; **Mats Svensson**, exceptionally multi-talented surgeon, always warmly supportive, and for those important long talks; and **Anders Hallin**, brother-in-arms, with outstanding surgical skill, and for radiating warm feelings to all people around him. And, all three, for valiantly covering so many nights and weekend shifts while I was doing other things.

**Lars Österlund**, dear friend, extraordinarily hard-working colo-rectal surgeon, and exceptional personality. For all those invaluable laughs, not in the least while sharing a one-room apartment for two years in Uppsala, and for always being able to see the comic side of events in life. Rock on!

**Anders Blomberg**, chief of surgery in Falun, for always showing great belief in me and instilling future aims.

**Anders Cohen**, former chief of surgery in Falun, for believing in, and helping to set up the first AAA screening program in Dalarna.

My room-mate, **Marcel Sadeghi**, skilled colo-rectal surgeon, experienced in life, and for those insightful long discussions of life in general.

**Daniel Klingberg**, trauma and general surgeon, for extending the privilege of being his tutor in surgery despite needing very little tutoring, and **Per**

**Wangefelt**, double-skilled urologist; both highly talented, and hardworking soon-to-be vascular surgeons at the vascular surgery team.

And, **Patrik Larsson**; surgical resident, for trusting me with tutorship and showing great promise.

**All my fellow surgeons at the department of surgery at Falu Lasarett**, for making going to work every day such a pleasant event and a continuously, thrilling experience. **And, all the highly professional staff at the entire department of surgery and operating theatres at Falu Lasarett.**

**All my fellow vascular surgeons at the section of vascular surgery at Akademiska Sjukhuset, Uppsala 2006-2007**; chief of vascular surgery **Krister Liungman**, vascular surgeons; **Björn Kragsterman**, **Johnny Steuer**, **Håkan Rudström**, **Gustaf Tegler**, and **Annika Boström Ardin**.

Professor **David Bergqvist**, for introducing me to scientific surgery. And, **Henrik Bengtsson**, vascular surgeon, who set me up with the first job in surgery at the department of surgery in Kristianstad 1994. Things would have been very different if we hadn't met.

Professor **Lars Wiklund**, former head of the department of surgical science, and professor **Olle Nilsson**, head of the department of surgical science, and associate professor **Ewa Lundgren**, former head of the department of surgery, Uppsala.

My closest family; my **Mother Gunilla** and my **Father Erik**, for delivering everything a childhood should include, teaching me the value of being brought up in the spirit of Rousseau, and love and encouragement. **Alf Lindholm**, my mother's *sambo*, for making my Mother happy. My brother **Tor**, for being a true friend, and his family; **Katriina**, **Oscar**, **Lovisa**, **Sofia**, and **Evelina**. My in-laws, **Helga and Lage Johannesson**, for always being there for my wife and me. And, my wife's brother, **Magnus**, and his family, **Lotta**, **Sara**, and **Victor**.

My closest of friends (in alphabetical order of appearance :) **Anna Broman Olasdotter**, **Stefan Hansson**, **Richard Henricsson**, and **Anders Lundgren**. And the families we like to spend so much time with in Falun; the family of **Anneli and Micke Strömsöe**, and the family of **Olle and Else-Maj Eriksson**.

Lastly, and utmost, my beloved wife **Lena**, and my beloved sons; **Joel**, **Emil**, and **Anton**. You are the epicentre of my life, around which everything revolves. What we have together is more than any man could wish for. I love you all dearly!

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“Cover picture”

The first Abdominal Aortic Aneurysm detected in the, at the time, newly implemented AAA screening programme in Dalarna. The individual was directly qualified for surgery of his unknown, large aneurysm, was repaired and made an uneventful recovery.

The photograph was kindly provided by Ewa Pihl, screening coordinator of the AAA screening programme in Dalarna, Falu Lasarett, Falun, Sweden.



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