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Abdominal Aortic Aneurysm

Experience from a Screening Study in Northern Sweden

BY

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Abstract

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Abdominal aortic aneurysm (AAA) is a common problem with life-threatening consequences and was suspected to be a serious health problem in Norsjö, a municipality in northern Sweden. A screening study was undertaken to investigate the prevalence, risk factors associated with AAA and the effect of screening on quality of life (QoL). All men and women, aged 65-75 years, were invited to an ultrasonography (US) examination, 91% attended and 92 subjects were also evaluated with computed tomography (CT).

Depending on diagnostic criteria, the AAA prevalence was 3.6-16.9% in men and 0.8-9.4% in women. Seventy-five percent of the differences between US- and CT anteroposterior measurements were less than 5 mm. A decrease in mental health was observed among AAA patients with low baseline SF-36 scale scores. Elevated cholesterol at age 60 years were associated with screening detected AAA after 12 years of follow-up. Smoking, atherosclerosis and having a first degree relative with AAA were associated with AAA at screening. Compared to blood samples obtained 12 years prior to screening an elevation of hsCRP over time was observed among AAA patients.

Based on a systematic review of the literature, different screening strategies were analysed in a Markov cohort model. The cost per life year gained ranged from \$8 309 to \$14 084 and was estimated to \$10 474 when 65 year old men were screened once.

Conclusions: The highest prevalence of AAA ever reported, in a population-based screening program, was found in Norsjö. The risk of having an AAA at screening showed a strong but complex association with atherosclerosis and its risk factors, genetic and inflammatory mechanisms may also be important. Screening 65-year-old men for AAA may be cost-effective, but QoL aspects on the cost-effectiveness of AAA screening merits further investigation.

Keywords: abdominal aortic aneurysm, definition, prevalence, ultrasonography, computed tomography, variability, quality of life, SF-36, risk factor, cholesterol, smoking, CRP, heredity, atherosclerosis, screening, cost-effectiveness, cost-utility

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To Åsa, Ida, Kalle and Erik

List of Papers

This thesis is based on the following papers, which are referred to in the text by the Roman numerals given below (I-V):

- I.** Wanhainen A, Björck M, Boman K, Rutegård J, Bergqvist D. The influence of diagnostic criteria on the prevalence of abdominal aortic aneurysm. *J Vasc Surg* 2001; 34: 229-235
- II.** Wanhainen A, Bergqvist D, Björck M. Intertechnique Differences in Measuring the Dimensions of the Abdominal Aorta: Comparison of Ultrasonography and Computed Tomography. *Eur J Vasc Endovasc Surg* 2002; 24: 428-434.
- III.** Wanhainen A, Rosén C, Rutegård J, Bergqvist D, Björck M. Low quality of life prior to screening for abdominal aortic aneurysm; a possible risk factor for negative mental effects. *Ann Vasc Surg* 2004 (*in press*).
- IV.** Wanhainen A, Bergqvist D, Boman K, Nilsson T, Rutegård J, Björck M. Factors associated with the development of abdominal aortic aneurysm. A study based on historical- and cross-sectional screening data. *Submitted*
- V.** Wanhainen A, Lundkvist J, Bergqvist D, Björck M. Screening for abdominal aortic aneurysm in men. An economic evaluation based on a systematic review of the literature. *Submitted*

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CONTENTS

INTRODUCTION	9
Historical notes	9
Epidemiology	11
Screening	17
AIMS OF THE INVESTIGATION	20
SUBJECTS, MATERIAL AND METHODS	21
Subjects, methodology and study design	21
Diagnostic criteria	27
Statistics and Ethics	28
RESULTS	30
Study I	30
Study II	34
Study III	36
Study IV	38
Study V	42
GENERAL DISCUSSION	45
Methodological aspects on AAA epidemiology	45
Prevalence of AAA	52
Risk factors for AAA	55
Screening for AAA	60
CONCLUSIONS	69
SUMMARY IN SWEDISH (Sammanfattning på svenska)	71
ACKNOWLEDGEMENTS	73
REFERENCES	75

ABBREVIATIONS

AAA	Abdominal aortic aneurysm
AP	Anteroposterior aortic diameter
BMI	Body mass index
BSA	Body surface area
CAD	Clinically acceptable difference
CHD	Coronary heart disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CVD	Cerebrovascular disease
HDL	High-density lipoprotein
hsCRP	High sensitive c-reactive protein
ISCVS	International Society for Cardiovascular Surgery
SVS	Society for Vascular Surgery
LDL	Low-density lipoprotein
Lp(a)	Lipoprotein (a)
LYG	Life year gained
Max	Maximum aortic diameter
OR	Odds ratio
PAOD	Peripheral artery occlusive disease
QALY	Quality adjusted life years
QoL	Quality of life
SD	Standard deviation
SF-36	Short-Form 36
Swedvasc	The Swedish Vascular Registry
TG	Triglyceride
TR	Transverse aortic diameter
US	Ultrasonography
VIP	Västerbotten Intervention Program
WHO	World Health Organization

INTRODUCTION

The term aneurysm comes from the Greek *aneurysma*, meaning a widening. Abdominal aortic aneurysm (AAA) thus means a widening or dilatation of the abdominal aorta. AAA is a common problem with life-threatening consequences. Most AAAs does not cause symptoms until late in their natural history, when they have the potential for spontaneous rupture. Ruptured AAAs represents an immediate emergency, with an overall mortality rate of 80-90% (Johansson 1994, Norman 1998, Semmens 1998, The UK Small Aneurysm Trial 1998, Adam 1999, Choksy 1999, Lindholt 2002, Ashton 2002, Vardulaki 2002) and causes 1% of all fatalities (Silverberg 1983, Vardulaki 1998), which in Sweden would be equivalent to about 1000 deaths each year.

A few AAAs have a specific cause, such as tertiary syphilis that once was an important cause, heritable connective tissue disorders such as Marfan's syndrome and Ehlers'-Danlos' syndrome or as a result from wall weakness after arterial dissection or infection. Most AAAs, however, are unknown in their etiology. Such an AAA was formerly considered to be an end-stage manifestation of atherosclerosis. Recent studies suggest that aneurysms and occlusive atherosclerosis are distinctly different disease processes (Tilson 1980, Lilienfeld 1987, Strachan 1991, Krohn 1992, Louwrens 1993, Patel 1995, Simoni 1996, Coggon 1996, Satta 1998, Blanchard 2000, Jamrozik 2000). AAA represents a degenerative process with degradation of important matrix proteins and today the term **nonspecific or degenerative AAA** is the proper descriptor, and is referred to in this thesis.

Historical notes

Although the problems and complications of aneurysm managements have been recognized for nearly 4000 years (Osler 1905), AAA was inaccessible to treatment until Sir Astley Cooper (1768 – 1841), in 1817, did the first attempt to ligate the infrarenal aorta in a man with a leaking iliac aneurysm. After seeing the patient in extremis he addressed the assembled students: "*Gentlemen, this only hope of safety I am determined to give him*". To which proposition the courageous patient replied: "*Sir I leave myself in your hands*". The abdomen was entered by an incision in the *linea alba*, and after blunt dissection Cooper is reported to have said: "*Gentleman, I have the*

pleasure of informing you that the aorta is now hooked upon my fingers". The patient, however, succumbed 40 hours after the operation (Cooper 1830).

A variety of techniques to treat AAA were introduced in the 19th century, all unsuccessful. Besides different techniques of ligation or banding (Reid 1926) also endoaneurysmorrhaphy (Matas 1903), wrapping (Abbot 1949) and wiring (Power 1921) the sac were tested. In the beginning of the 20th century important steps were taken: The development of techniques on suturing blood vessels (Carrel 1905), replacement of a human artery (Goyanes 1988), and angiographic visualization of the abdominal aorta (Dos Santos 1929). Following World War II the progress was rapid. The importance of blood replacement and the value of antibiotics were recognized and heparin was introduced. The final conclusive progress was the development of vascular grafts. Robert Gross was the first to use harvested, preserved homografts for treatment of coarctation of the aorta (Gross 1945).

Two years later, in 1950, Jacques Oudot performed the first successful resection and homograft replacement of an occlusion of the aortic bifurcation (Oudot 1951). In 1951, the first successful reconstruction of an AAA was done by **Freeman and Leeds** (Freeman 1951). Two years later Henry Bahnson performed the first successful repair of a ruptured AAA (Bahnson 1953). Due to serious deterioration of structural integrity, the use of human homograft implantation was replaced by synthetic prostheses. Knitted Dacron graft (DeBakey 1958) and the inlay technique leaving the aneurysmal sack in situ (Orr and Davies 1974) became the golden standard of AAA resection until today (Zarins 1997).

One of the most famous patients who died of a ruptured AAA was Albert Einstein. His comment when his AAA ruptured in 1954 is important to bear in mind when dealing with this challenging condition: *"I want to go when I want. It is tasteless to prolong life artificially. I have done my share, it is time to go. I want to do it elegantly"* (Cohen 1990).

In the last two decades, endovascular deployment of stent graft was developed. After the first experience by Volodos and following Juan Parodi's first report in the English language in 1991, the technique has attracted much interest (Volodos 1991, Parodi 1991). The long-term results of the first generation of stent grafts were, however, disappointing (Guidoin 2000, Holzenbein 2001). Although the durability of the second generation of stent grafts is not known, the technique has several advantages over standard open surgery.

Epidemiology

Epidemiology is the science concerned with the study of factors determining and influencing the frequency and distribution of diseases and their causes in a defined human population for the purpose of establishing programs to prevent and control their development (Dorland 1988). It is one important approach to obtaining the kind of information clinicians need to make good decisions in the care of patients (Fletcher 1996).

Definition of AAA

Before establishing the occurrence of a disease, **diagnostic criteria** must be defined. There is, however, no general agreement on how to define an AAA. The proposed definitions are all based on the diameter of the abdominal aorta (McGregor 1975, Sterpetti 1987, Collin 1988, Johnston 1991).

In 1965 Steinberg and Stein established normal standards for abdominal aortic diameters (Steinberg 1965). They concluded that a diameter in excess of 30 mm was well above the average for both sexes and was considered to be the dividing line between ectasia and aneurysms (Steinberg 1966). This was the basis for the most accepted **definition**, later described by McGregor in 1975, defining an AAA as the maximum infrarenal aortic diameter being 30 mm or more (McGregor 1975).

The ratio between the infrarenal diameter and the suprarenal diameter was found to be the most important factor regarding expansion (Sterpetti 1987). Two proposed definitions relate the infrarenal aortic diameter to the suprarenal aortic diameter: A maximum infrarenal aortic diameter being 1.5 times larger or more than the suprarenal aortic diameter (Sterpetti 1987) and a maximum infrarenal aortic diameter being 40 mm or more or infrarenal aortic diameter exceed suprarenal aortic diameter by at least 0.5 cm (Collin 1988).

Several authors have clarified that the diameter of the abdominal aorta depends on age, sex and body surface area (BSA) (Pearce 1993, Sonesson 1994, Grimshaw 1997) and a nomogram for prediction of the normal aortic diameter, depending on these factors, was developed (Sonesson 1994). The definition proposed by the ISCVS/SVS Ad Hoc Committee, where an AAA is defined as the maximum infrarenal aortic diameter being at least 1.5 times larger than the expected normal infrarenal aortic diameter (Johnston 1991), may compensate for such individual variation.

Besides these four main definitions different fix diameters, such as 25 mm (O'Kelly 1989, McCarthy 2003) or 35 mm (Bengtsson 1991, Pleumeekers 1995) as well as different ratios of infrarenal to suprarenal diameter such

as 1.2 or more (Alcorn 1996) have been used. In some reports, “a bulging” of the infrarenal aorta has been used to define an AAA (Bengtsson 1991).

Diagnostic techniques

The knowledge on the epidemiology of AAA increased dramatically in the last two decades. Previous **diagnostic techniques** such as plain X-ray and abdominal palpation have severe limitations in detecting AAA (Collin 1988, Lederle 1988). With the introduction of noninvasive diagnostic techniques such as **computed tomography** (CT) and **ultrasonography** (US) it became possible to investigate populations for the presence of clinically unknown AAA with diagnostic accuracy (Gomes 1987).

There is, however, no golden standard for measuring the aortic diameter (Lederle 1995, Jaakkola 1996). In the majority of published studies, US was used for practical and economic reasons (Bengtsson 1989). US has emerged as the most practical method for screening and follow-up of infrarenal abdominal aortic aneurysms (AAA) while CT has become the preferred preoperative technique. However, significant intra- and interobserver variability was reported for both US and CT (Gomes 1987, Bengtsson 1989, Ellis 1991, Akkersdijk 1994, Thomas 1994, Lederle 1995, Jaakkola 1996, Singh 1998, Aarts 1999, Singh 2003). Furthermore, some of the described definitions require the suprarenal aortic diameter to be measured, which can be difficult with US (Gomes 1978, Ellis 1991).

Prevalence and rupture incidence

Necropsy reports provided the first information on AAA epidemiology (Manigila 1952). The main shortcoming with most necropsy studies is selection bias due to a low autopsy rate (Bengtsson 2000). One important exception is the large study from Malmö, Sweden. Based on more than 45.000 autopsies over a 30 years period and a very high necropsy rate, 85% of all deaths in the community and more than 90% of all hospital deaths, the age- and sex- specific frequency was reported (Bengtsson 1992). AAA is uncommon before the age of 55 in men. The **prevalence** then increases rapidly reaching a peak of about 6% at 80-85 years. In women AAA appears 10-15 years later and is 2-4 times less common than in men. Over the study period, an increase of the age-standardized prevalence was observed.

All studies on **the incidence of AAA rupture** are retrospective and based on routine mortality statistics (Bengtsson 1993). The validity of these registers is often poor (Elffors 1988, Johansson 1988, Drott 1991), which may explain the large differences in reported rupture incidences between studies. In Malmö, the rupture incidence was 5.6/100.000 individuals (8.4/100.000 men and 3.0/100.000 women). The age specific incidence peaked at

112.7/100.000 men aged 80-89 years and 67.6/100.000 women aged 90 or above. However, the largest number of ruptures was seen a decade earlier. The overall mortality due to ruptured AAA was 88% (Bengtsson 1993). The Malmö registry was based on a high autopsy rate using standardized technique and registration procedures, including definition of the disease (Sternby 1968, Bergqvist 1985)

The Oxford screening programme was the first **population-based screening study** (Collin 1988). In the last two decades several large-scale population-based screening studies using US have given us a good picture of the epidemiology of AAA. The findings are in accordance with the autopsy findings reported from Malmö (Bengtsson 1992) with the prevalence varying from 4.3 to 8.8% in general populations (Collin 1988, Bengtsson 1991, Smith 1993, Holdsworth 1994, Morris 1994, Scott 1995, Simoni 1995, Ögren 1996, Grimshaw 1997, Lindholt 1997, Lederle 1997, Boll 1998, Vasquez 1998, Wilmink 1999, Jamrozik 2000, Kyriakides 2000, Newman 2001, Lederle 2002, MASS 2002, McCarthy 2003). Most screening detected AAAs are small, 70% are less than 40 mm (Scott 1994, Lederle 2000, Wanhainen 2001, Ashton 2002, McCarthy 2003).

Natural course and surgical outcome

The **natural course** of AAA includes aspects on the characteristics of the aneurysm as well as of the patient carrying the disease. To investigate the true natural history of AAA would require no intervention, which is ethically impossible. Information obtained from studies of small AAA (Guirguis 1991, Bengtsson 1993, Brown 1996, Lindholt 2000, Lederle 2002, MASS 2002, Biancari 2002) or patients unfit for surgery (Fielding 1981, Limet 1991, Lederle 2002, Brown 2003) is the only available. However, due to differences in the studied populations the information provided is incomplete. The natural course of AAA is to gradually **expand** and eventually to **rupture**.

The expansion pattern has been shown to be exponential rather than linear, estimated to about 10% per year (Limet 1991, Bengtsson 1993, Brown 1996, Stonebridge 1996, Vardulaki 1998). The average expansion rate has been calculated to approximately 0.3-0.5 cm per year (Bengtsson 1993, Stonebridge 1996, The UK Small Aneurysm Trial 1998). However, a large individual variation in expansion pattern was observed with episodes of sudden, rapid expansion followed by periods of slower expansion and some AAAs may even decrease their diameter (Nevitt 1989, Guirguis 1991, Bengtsson 1993). The factors that influence the progression of AAA may partly be different from those responsible for the initiation of the disease. In addition to the initial diameter, rapid expansion is associated with age, smoking and hypertension (Cronenwett 1990, Chang 1997).

Thirteen percent of all AAAs eventually rupture (Bengtsson 1992). The risk of aneurysm rupture is in proportion to the aneurysm size. Small AAAs, less than 50 mm, have a very low rupture rate, whereas the rate of rupture is approximately 5-10% per year for AAAs between 50 to 60 mm and more than 10% for AAAs larger than 60 mm (Nevitt 1989, Limet 1991, Guirguis 1991, Bengtsson 1993, Scott 1998, The UK Small Aneurysm Trail 1998, Choksy 1999, Lederle 2002, Brown 2003, McCarthy 2003). In addition to AAA diameter, female sex, a positive family history, smoking, hypertension and chronic obstructive pulmonary disease (COPD) are associated with an increased risk of rupture. The expansion rate and the ratio of infrarenal to suprarenal diameter may affect the rupture risk (Cronenwett 1985, Darling 1989, Sterpetti 1991, Verloes 1995, Lobato 1998).

With better patient selection and medical improvement the **operative mortality** has gradually decreased over the last decades (Bickerstaff 1984, Chen 1997). The relative reduction is larger for elective surgery than for surgery for ruptured AAA (Chen 1997). A review of recent population-based and multicentre studies found an average operative mortality of 5.3% (Wen 1996, Kazmers 1996, Koskas 1997, Norman 1998, The UK Small Aneurysm Trial 1998, Semmens 1998, Galland 1998, Dardik 1999, Lawrence 1999, Heller 2000, Huber 2001, Ashton 2002, Lederle 2002) and based on mortality reported in the nationwide Swedish vascular database a mortality of 3.1% was seen after surgery for non-ruptured AAA during the last 3 years (Swed-vasc 2003). Independent risk factors for operative mortality after elective repair are renal dysfunction, congestive heart failure and ischemic heart disease, pulmonary dysfunction, age and female gender. The operative mortality increases with the number of co-morbidities present, and is reported to be 40% if cardiac, renal and pulmonary diseases were present simultaneously (Steyerberg 1995). The surgeon's training and both surgeon and hospital volume of AAA repair are also important factors influencing the mortality (Berridge 1995, Kazmers 1996).

The operative mortality for ruptured AAA is approximately 40% in recent reports. However, most patients, approximately 2/3, with ruptured AAA die without coming to surgery. Thus, the overall mortality is about 80% (Vardulaki 1998, Semmens 1998, Norman 1998, The UK Small Aneurysm Trial 1998, Adam 1999, Choksy 1999, Lindholt 2002, Ashton 2002, Vardulaki 2003). The main factor predicting death after surgery for ruptured AAA is the degree of shock at arrival to operating room (Halpern 1997). The degree of specialization of the surgeon may also have a role in determining survival after a ruptured AAA. In a study from Wales the average operative mortality did not differ significantly between vascular surgeons and general surgeons. However, vascular surgeons operated on a significantly larger proportion of patients admitted with ruptured AAA, and consequently the overall survival differed significantly, 35 vs. 11 % (Basnyat 1999). In an

analysis within the Swedvasc the peri-operative mortality was significantly improved if the surgeon was trained in vascular surgery (Swedvasc 1998).

Due to co-morbidity patients with AAA have an increased mortality compared to a general aged-matched population, unrelated to the AAA. The relative survival is estimated to 90% after 5 years (Johansson 1990, Olsen 1991, Stonebridge 1993, Johnston 1994, Johnston 1994, Aune 1995, Norman 1998, Cho 1998). **Long-term survival** does not differ significantly after successful repair of ruptured compared with non-ruptured AAA (Fielding 1981, Roher 1988, Stonebridge 1993, Norman 1998) and the most frequent cause of death after AAA surgery is coronary artery disease (Hollier 1984, Vohra 1990). Survivors have generally good **quality of life** (QoL). Several investigations have found that the diagnosis has a negative influence on QoL and that surgery improves QoL compared to surveillance (Hennessy 1998, UK Small Aneurysm Trial 1998, Perkins 1998, Lindholt 2000, Malina 2000, MASS 2002, Joseph 2002). However no information on **quality adjusted life years** (QALY) is available.

Knowledge of the natural course of AAA is fundamental in **surgical decision-making**. Patients with ruptured AAA do not survive without operative repair, thus making decision-making more straightforward. For asymptomatic cases however, the process is more complex. Three key variables have to be considered: elective operative risk, the risk of AAA rupture and life expectancy. Based on these factors the threshold diameter for elective repair is estimated. In selected cases an AAA diameter of 50 – 55 mm generally justifies elective repair (The UK Small Aneurysm Trial 1998, Lederle 1998). However, an individual approach is recommended. For older patients and patients with important co-morbidity the threshold diameter is greater, and 12-25% of the patients are considered unfit for surgery (Johansson 1990, The UK Small Aneurysm Trial 1995, Valentine 2000, Lindholt 2002, Vardulaki 2002).

Risk factors and risk groups

Several cross-sectional screening studies (Krohn 1992, Pleumeekers 1995, Simoni 1995, Kanagasabay 1996, Jamrozik 2000, Vardulaki 2000, Lederle 2000, Singh 2001) and a few prospective population-based studies (Alcorn 1996, Rodin 2003) have established male gender, age, smoking and a positive family history of AAA as independent **risk factors** for AAA.

Although several studies have revealed a strong association between AAA and atherosclerotic diseases, reports on possible associations between AAA and established risk factors for atherosclerosis, such as hypercholesterolemia and hypertension, have shown divergent results (Strachan 1991, Krohn 1992, Louwrens 1993, Pleumeekers 1995, Simoni 1995, Kanagasabay 1996, Alcorn 1996, Simoni 1996, Lee 1997, Naydeck 1999, Blanchard 2000, Jamrozik 2000, Vardulaki 2000, Lederle 2000, Newman

2001, Tornwall 2001, Singh 2001, Rodin 2003). Histological and epidemiological differences between AAA and atherosclerosis have further challenged the traditional theory of AAA as being a manifestation of atherosclerosis (Lilienfield 1987, Norman 1991, Patel 1995, Satta 1998).

Screening studies have identified several risk groups. AAA is 2-4 times more common in men than in women (Scott 1995, Newman 2001, Lederle 2002). A high prevalence was found among close relatives of AAA patients, smokers and among patients with occlusive arterial disease (Bengtsson 1988, Bengtsson 1989, Webster 1991, Adamsson 1992, Adams 1993, Moher 1994, Jaakkola 1995, Fitzgerald 1995, Lindholt 1997). The highest prevalence was observed in patients with popliteal aneurysm, among whom about 50% also have an AAA (Vermilion 1981, Whitehouse 1983, Anton 1986).

The Norsjö municipality

The Norsjö municipality, situated in the inland part of the Västerbotten province in northern Sweden, *figure 1*, was found to have a high mortality in cardiovascular disease. The cardiovascular disease death rate for all ages was 56/10.000 in men and 43/10.000 in women (Eriksson 1981).

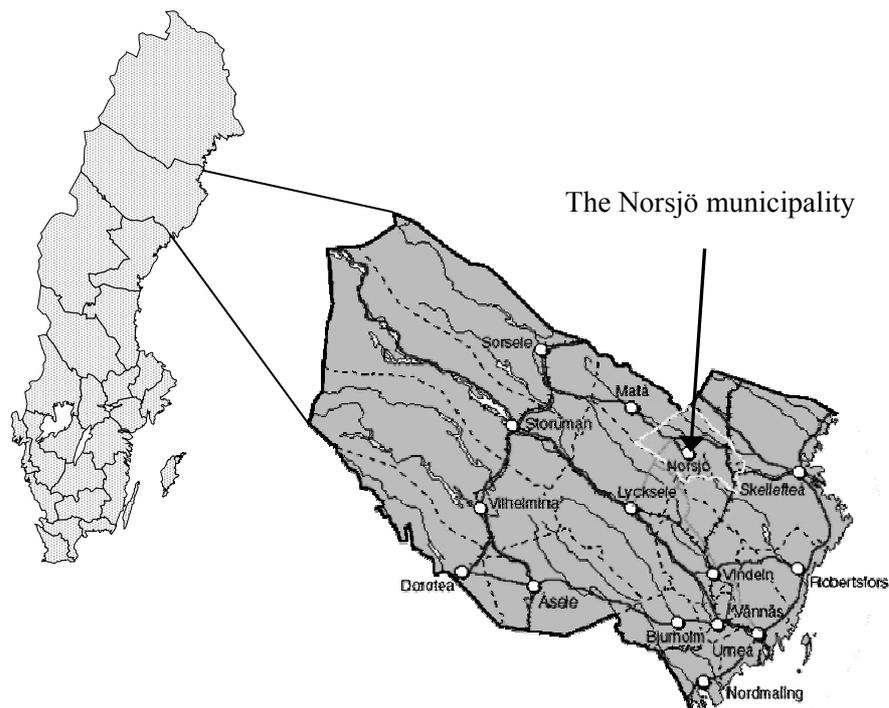


Figure 1. The Norsjö municipality, situated in the inland part of the Västerbotten province in northern Sweden

In the past the employment in the Norsjö municipality was characterised by heavy physical work in forestry, agriculture and mining and the daily food intake was based on milk, flour, sausages and a special form of “American” bacon. This physical work had, however, diminished during recent decades, while eating tradition were more persistent (Weinehall 1997).

Compared with other industrialised societies, the population in northern Sweden had higher serum cholesterol levels, lower HDL levels in men and intermediate blood pressure levels. The prevalence of cigarette smoking in men was relatively low and marked obesity was less prevalent than in other communities (Huhtasaari 1988).

An ongoing community intervention programme concerning cardiovascular disease and diabetes, the Västerbotten Intervention Program (VIP) started in Norsjö as the Norsjö Health Programme in 1984 (Västerbottens Läns Landsting 1984). As part of this program all men and women are invited to a health survey at their local health center the year they become 30, 40, 50 and 60 years old. Blood pressure, height and weight were measured. The participants were asked whether they accepted to donate fasting blood samples to be stored at the Northern Sweden Medical Research Bank for future research purposes and to fill in a questionnaire with items on, among others, smoking habits, medical history and intake of drugs.

At Skellefteå County Hospital, that serves the Norsjö municipality, approximately twice as many patients were operated on for AAA than was expected from the population in the catchment area. The incidence of AAA-surgery was 17.8/100.000/year in Skellefteå compared to 10.7/100.000/year in Sweden as a whole. The corresponding emergency operation incidence was 11.0/100.000/year and 4.1/100.000/year respectively (Bergqvist 1998, Björck 2000). Many of the patients came from Norsjö, and a high prevalence of AAA was therefore suspected.

Screening

The best therapy for AAA is presymptomatic, elective surgery in appropriately selected individuals. However, most AAAs are undiagnosed and a majority of patients with ruptured AAA die without surgery (Vardulaki 1998, Semmens 1998, Norman 1998, The UK Small Aneurysm Trial 1998, Adam 1999, Choksy 1999, Lindholt 2002, Ashton 2002, Vardulaki 2003). To reduce the high mortality, early detection by screening has been advocated (Budd 1989, Basnyat 1999, Beard 2003, Swedenborg 2003, Frame 2004, Greenhalgh 2004, Earnshaw 2004).

Screening is, according to the World Health Organization (WHO), defined as a medical investigation that does not arise from a patient’s request for advice for specific complains. The question of whether or not screening programmes for AAA are worthwhile is controversial (Bergqvist 1999). The

evaluation includes assessment of mortality, **health economy** and influence on QoL. Recently, a number of careful studies have demonstrated that screening for AAA in elderly men can reduce AAA rupture rate by 49-70% (Vardulaki 2002, Lindholt 2002, MASS 2002, Wilmink 2003). However, important aspects need to be further analysed. WHO has defined the following basic criteria for a medical screening programme to be acceptable (Wilson and Jungner 1968):

1. **The disease is an important health problem.** AAA causes about 1000 deaths each year in Sweden, which represents 1% of all deaths (Silverberg 1983, Vardulaki 1998). In elderly men AAA may cause as many as 2% of all deaths (Earnshaw 2004).
2. **There is a generally accepted treatment.** The golden standard is surgical treatment with intraluminal graft replacement of the AAA (Zarins 1997). Elective AAA repair is one of the most frequent vascular surgery procedures with a perioperative mortality less than 5% (Swedvasc 2003).
3. **Provisions for diagnosis and treatment are available.** The screening strategy may affect the demand of resources. The most probable scenario is to screen men once at the age of 65, which the health organization of today could handle (Swedenborg 2004). However, different screening strategies need to be analyzed.
4. **The disease must have a detectable latent stage.** The risk of aneurysm rupture is in proportion to the aneurysm size. Most screening detected AAAs are small and have a low risk of rupture (Nevitt 1989, Limet 1991, Guirguis 1991, Bengtsson 1993, Scott 1998, The UK Small Aneurysm Trail 1998, Choksy 1999, Lederle 2002, Brown 2003, McCarthy 2003).
5. **A suitable screening method must be available.** The screening method should not only show a high diagnostic accuracy but should also be rapid, inexpensive and safe. US is a noninvasive test that fulfills all these criteria.
6. **The screening method must be accepted by the target population.** US has proven to be well accepted in several population-based screening studies. The attendance rate is often above 75% (Collin 1988, Bengtsson 1991, Smith 1993, Holdsworth 1994, Morris 1994, Scott 1995, Simoni 1995, Ögren 1996, Grimshaw 1997, Lindholt 1997, Lederle 1997, Boll 1998, Vasquez 1998, Wilmink 1999, Jamrozik 2000, Kyriakides 2000, Newman 2001, Lederle 2002, MASS 2002, McCarthy 2003).
7. **The natural cause of the disease must be known.** The most important factors predicting rupture is aneurysm diameter and expansion rate. AAAs less than 55 mm have a low risk of rupture (Nevitt 1989, Limet 1991, Guirguis 1991, Bengtsson 1993, Scott 1998, The UK Small Aneurysm Trail 1998, Choksy 1999, Lederle 2002, Brown 2003, McCarthy 2003).

8. **The policy for treatment of the disease must be clear.** The UK small aneurysm trial and the ADAM-study have demonstrated the safety with surveillance until the AAA-diameter reach 55 mm (The UK Small Aneurysm Trial 1998, Lederle 1998).
9. **The cost effectiveness of a screening program must be reasonable.** Most previous studies on cost-effectiveness have found screening 65-year-old men to be cost-effective (StLeger 1996, Wilmink 1999, MASS 2002, Lee 2002, Lindholt 2002, Boll 2003). However, they are heterogeneous concerning several important criteria making it difficult to compare the results. There are only a few prospective studies concerning cost-effectiveness, and they all have a short follow-up (Wilmink 1999, MASS 2002, Lindholt 2002). Furthermore, different screening strategies need evaluation.
10. **The treatment of the disease should favour prognosis of patients.** The overall mortality after ruptured AAA is extremely high and pre-symptomatic, elective surgery in appropriately selected individuals will prevent rupture, and thereby improve life expectancy. Long-term survival after successful AAA repair is only slightly shorter compared to the general aged-matched population (Johansson 1990, Olsen 1991, Stonebridge 1993, Johnston 1994, Johnston 1994, Aune 1995, Norman 1998, Cho 1998). There is, however, a possible negative effect on QoL (Hennessy 1998, UK Small Aneurysm Trial 1998, Perkins 1998, Lindholt 2000, Malina 2000, MASS 2002, Joseph 2002), and the consequences of this decrease need characterization.

AIMS OF THE INVESTIGATION

The overall aim of this investigation was to evaluate different aspects of screening for AAA, emerging from the experience of a screening study in the Norsjö municipality, where AAA was suspected to be a major health problem.

The specific aims were:

To study the prevalence of AAA in the Norsjö municipality (Study I)

To analyze the influence of different diagnostic criteria, age and sex on the reported prevalence of AAA. (Study I)

To examine the difference and variability between US and CT in measuring the abdominal aorta. (Study II)

To investigate factors associated with development of AAA in the Norsjö municipality (Study IV)

To study interactions between factors associated with AAA. (Study IV)

To assess the cost-effectiveness of different screening strategies for AAA in a decision analysis model (Study V)

To identify the most important variables affecting the cost-effectiveness of screening for AAA in sensitivity analyses (Study V)

To evaluate the effect of screening for AAA on QoL. (Study III)

To assess the cost-utility of screening for AAA (Study V)

To identify critical areas where more information is needed to be able to assess the cost-effectiveness of screening for AAA. (Study V)

SUBJECTS, MATERIAL AND METHODS

Subjects, methodology and study design

Study I

In a population-based screening study, all men and women aged 65 to 75 years in Norsjö municipality were invited to take part in an US examination at the local health centre. On the 1st of January 1999, 555 inhabitants of Norsjö municipality were 65-75 years of age, 11.6% of the total population of 4804. Those with an aortic diameter of ≥ 28 mm and/or with poor US visibility were invited to an evaluation with computed tomography (CT), *figure 2*.

Study II

In a descriptive cross-sectional study, 61 subjects (33 with an AAA and 28 with a non-aneurysmal aorta) were investigated with US and CT, *figure 2*. The differences and variabilities were analysed for anteroposterior (AP) and transverse (TR) diameters.

The analysis technique proposed by Bland and Altman (Bland 1986) was used, where the estimated bias between US and CT is the mean difference (US diameter–CT diameter) and the standard deviation (SD) of the differences measure random fluctuations (variability) around this mean.

The variability was reported as 95% limits of agreement (mean difference $\pm 1.96 \times$ SD), which tell us how far apart measurements by the two techniques are likely to be for most individuals. The concept of “clinically acceptable difference” (CAD) was used to express the proportion of differences less than 5 mm (Jaakkola 1996).

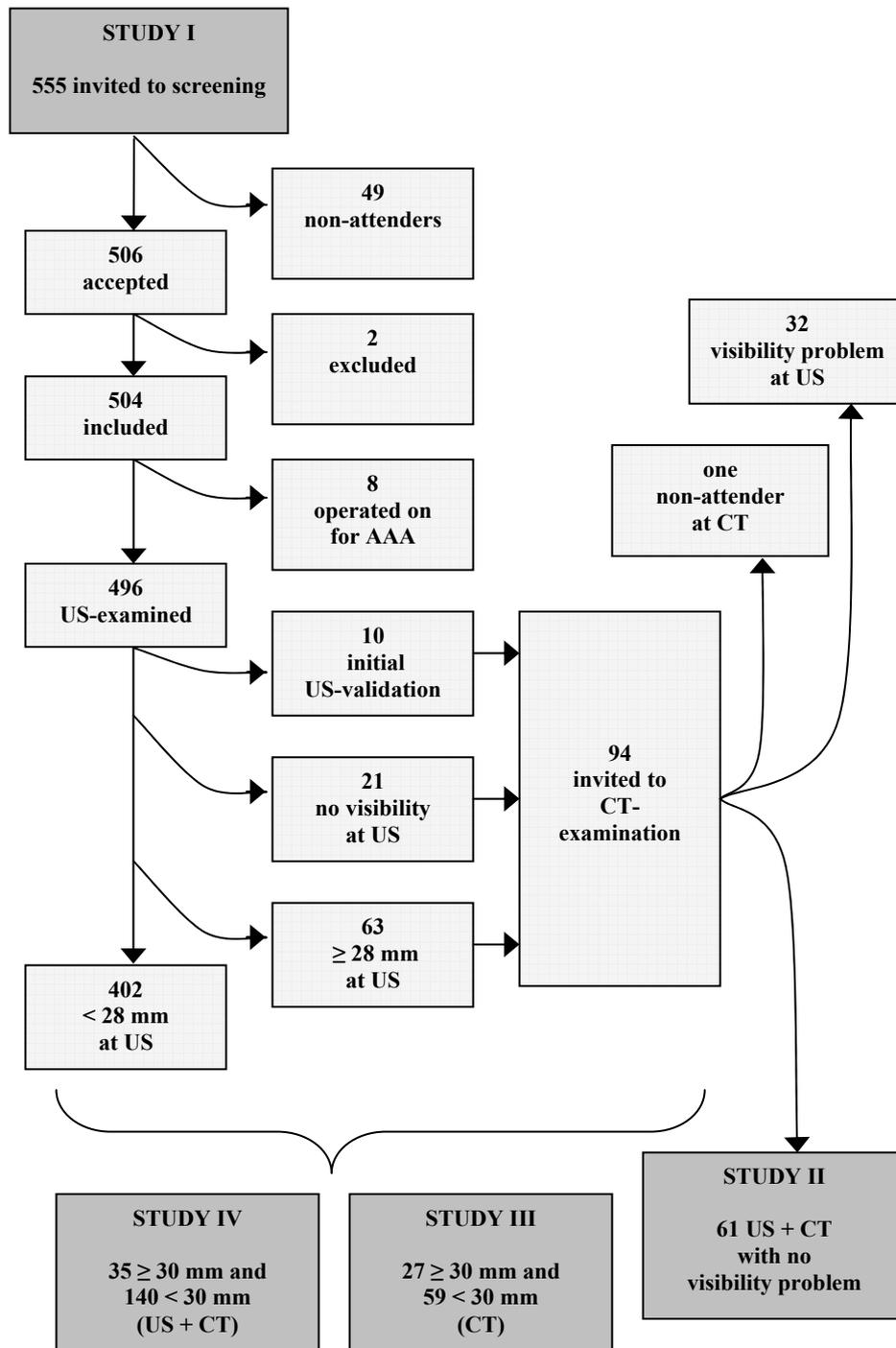


Figure 2. Overview of the study population in papers I – IV.

Study III

In a prospective controlled population-based study, all participants were asked to complete a questionnaire before screening and 27 patients with screening detected AAA and 59 randomly selected age- and sex-matched persons (controls) with normal aortic diameter were asked to complete a questionnaire 12-months after screening.

Comparisons were made between the two groups (AAA-group and control-group), within each group and between the groups and with norms for the general Swedish population in the same age-interval

QoL was measured with Short-Form 36 (SF-36), a validated self-administration questionnaire composed of 36 items. Each item is used in scoring one of eight scales, which forms two clusters, physical and mental health, *table 1*. Scale scores range from 0 (negative health) to 100 (positive health). In addition to SF-36, ten AAA-specific questions were included in the 12-months evaluation of the AAA-group (table 4, page 20 in study III).

Comment

The study group in study III was recruited from the screening study (study I), as shown in figure 2. Among the 35 patients with AAA in Study I, defined as an aortic diameter ≥ 30 mm by means of CT, 27 were included in Study III. The reason that eight patients were not included was that the original study-design included measurement of QoL at one month after screening. Due to a certain delay in CT-examinations some subjects had an uncertain diagnosis one month after screening and they were excluded from this study.

Table 1. Summary of SF-36 profile with eight multi-item scales and two dimensions (clusters) and the extent (validity) to which the scales influence the clusters

Scale	Abbreviation	Dimension (cluster)	
		Physical (PHC)	Mental (MHC)
Physical Functioning	PF	***	*
Role-Physical	RP	***	*
Bodily Pain	BP	***	*
General Health	GH	**	**
Vitality	V	**	**
Social Functioning	SF	**	***
Role-Emotional	RE	*	***
Mental Health	MH	*	***

*** = substantial, ** = moderate, and * = weak validity

Study IV

In a population-based case-control study, factors associated with AAA were analysed in 35 cases and four randomly selected sex- and age-matched controls assigned to each one of them, *figure 2*. Three sets of data were analysed; 1) data obtained at the VIP-survey, when the participants were at the age of 60 years (historical data), 2) data obtained at the AAA-screening, when subjects were at age 65 to 75 years (cross sectional data), 3) differences between cross sectional- and historical data (Δ data). The mean time between assessments of historical- and cross sectional data was 11.6 years. Variables assessed at different time are displayed in *table 2*.

Table 2. Overview of factors assessed in study IV.

	Historical data**	Cross-sectional data***	Δ data****
Age*	X	X	X
Sex*		X	
Height, weight, BMI	X	X	X
Smoking habits, Snuff		X	
Blood pressure	X		
Hypertension		X	
Coronary heart disease		X	
Cerebrovascular disease		X	
PAOD		X	
Diabetes mellitus		X	
Family history of AAA		X	
Creatinine	X	X	X
Cholesterol	X	X	X
Lp(a)	X	X	X
Triglycerides	X	X	X
HsCRP	X	X	X

* Separate unmatched analyses were performed to evaluate the association of sex and age with AAA

** Data obtained at VIP-survey at age 60 years.

*** Data obtained at AAA-screening study at age 65-75 years

**** Difference over mean time 11.6 years (cross-sectional data – historical data)

Study V

In a Markov cohort simulation model, two hypothetical groups of persons were compared: one group invited and another not invited to ultrasound screening. The cost per life year gained (LYG) was the main outcomes measure and cost per QALYs a secondary outcome measure. The base case analysis assumed a strategy where 65 year-old Swedish men were invited

once for screening. The model follows a cohort of patients from the time of screening until death or 100 years of age. The model structure is displayed in *figure 3*.

Other screening strategies with different assumptions of the age of the screened population (60-70 years), risk profiles (smokers, siblings of AAA-patients, persons with angina or claudication and patients with popliteal aneurysm) and introduction of re-screening (after 5 or 10 years) were also analysed. The various strategies were assumed to differ from the base case assumptions in the prevalence of AAA, the mortality and in cost for screening.

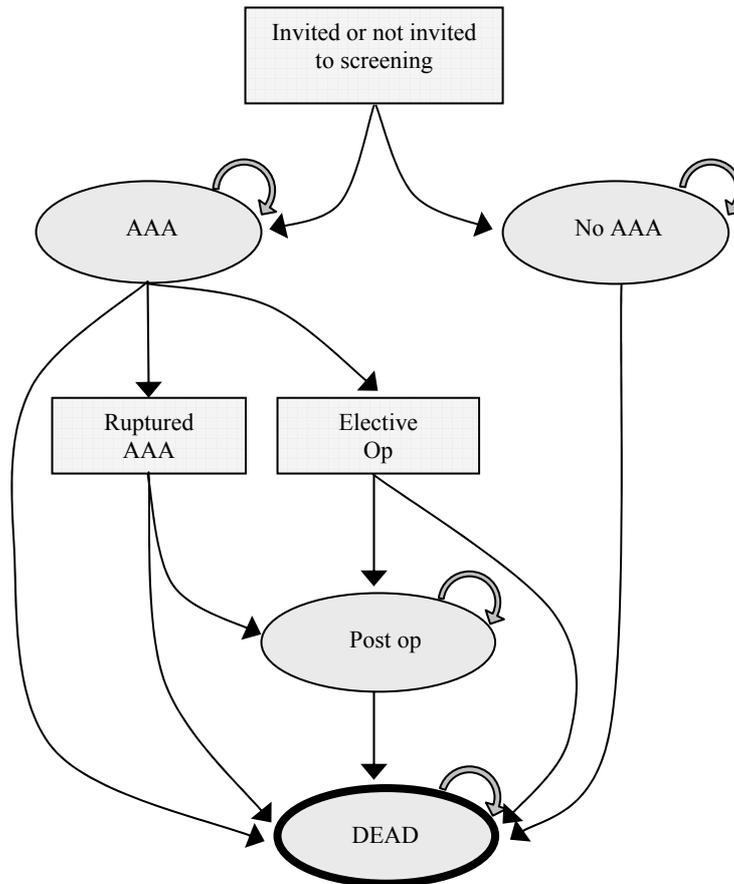


Figure 3. The Markov model structure. Each circle represents a Markov state. The circle labeled “DEAD” represents an absorbing state, from where a person cannot leave. Arrows indicate allowed transitions. The transition probabilities differ between the two groups; invited or not invited to ultrasound screening.

Pooled results from a systematic review of the literature were used to estimate parameters in the model. The selection criteria in the literature review are listed in *table 3*. The estimated parameters in basecase are listed in *table 4* and in riskgroups in *table 5*.

Table 3. Selection criteria in the literature review

1	Population-based or multicentre studies
2	Original clinical research report
3	Published after 1990
4	Written in English language
5	AAA defined as infrarenal diameter 30 mm or more
6	Male sex specific data should be available
7	The age distribution of the patients should be described
8	The follow-up period should be given
9	The proportion not participating, unfit for surgery and lost to follow-up should be given
10	A distinction between surgery for ruptured and non-ruptured AAA should be possible

Table 4. Estimated parameters in basecase

Assumption	Probability (SD) #	
	Screening	No screening
Probability of a positive screening / prevalence	5.5% (0.09)	
Proportion qualified and fit for surgery directly	6.8% (0.09)	-
Attendance rate	80%	-
AAAs yearly risk for non-ruptured AAA surgery	3.9% (0.09)	1.4% (0.05)
Proportion of opportunistically detected AAA	-	13% (0.15)
Mortality for non-ruptured AAA surgery	3.1% (0.42) and 5.3% (0.04)	
Rupture risk of an AAA / year	0.8% (0.04)	1.9% (0.06)
Ruptured AAA mortality before surgery	65% (0.96)	
Ruptured AAA operative mortality	40% (0.83)	
AAA patient relative survival	90% (0.56) / 5 years*	
Cost of invitation	\$5.6	-
Cost of screening	\$54.6**	-
Cost for traveling to the screening	\$5.6***	-
Cost of follow-up	\$242.4	
Cost of elective AAA surgery	\$16 831	
Cost of surgery of ruptured AAA	\$32 183	

* Equal to 2.05 times the normal mortalities both before and after surgery of AAA.

Normal death rates based on population mortality statistics for Swedish males.

** Only incurred by attenders. A one time cost of \$187.5 for a physician visit was added for those with AAA for informing the patients about the disease.

*** Only incurred by attenders.

For references se paper V, page 4-6.

Table 5. Risk group assumptions

Risk population	AAA prevalence	Mortality risk*
65-year-olds	5.5%	2.05
Current smokers	9.5%	2.6
Siblings	18.6%	2.05
Angina or claudication	10%	2.5
Popliteal aneurysm	50%	2.5
60-year-olds	3.4%	2.05**
70-year-olds	6.1%	2.05**
Re-screening of 65-year-olds after 5 years	2.2%***	2.05
Re-screening of 60-year-olds after 5 years	2.9%***	2.05**
Re-screening of 60-year-olds after 10 years	4.2%***	2.05**

* Relative risk in persons with AAA, compared to the general population

** General population mortalities adjusted to correspond to 60- and 70-year-olds

*** The prevalence of new AAA detected at the re-screening. All new AAA were assumed to be less than 55 mm.

Diagnostic criteria

Four different definitions of AAA were used in study I, *table 6*. In study II-V an AAA was defined as proposed by McGregor.

Table 6. Definitions of infrarenal AAA

Nr	Author	Definition
1.	McGregor	Aortic diameter \geq 30 mm
2.	Sterpetti	Aortic diameter \geq 1.5 x suprarenal aortic diameter
3.	Collin	Aortic diameter \geq 40 mm or infrarenal aortic diameter exceeding suprarenal aortic diameter by at least 0.5 cm
4.	ISCVS / SVS*	Aortic diameter \geq 1.5 x normal infrarenal aortic diameter, predicted from a nomogram

* International Society for Cardiovascular Surgery / Society for Vascular Surgery

The definitions proposed by Sterpetti and Collin requires imaging of the suprarenal aortic diameter. Such measurements were considered unreliable with US and therefore a CT was performed in subjects in whom the abdominal aorta was 28 mm or more at the initial US. A nomogram (Sonesson 1994) for prediction of the normal aortic diameter using age, sex and body surface area was used. The body surface area was calculated using Du Bois' formula (body surface area, $\text{cm}^2 = \text{weight}^{(0.425)}$, kg x $\text{height}^{(0.725)}$, cm x 71.84).

In study I, the prevalence of disease was calculated for US and CT, using both maximum diameter and maximum anteroposterior diameter. Based on the fact that all aneurysms with a diameter 50 mm or more met the criteria of the four definitions used and all were considered to have a normal suprarenal aortic diameter at surgery these were included in the prevalence regardless of definition. In study II and III the definition of an AAA was based on the maximum diameter by means of CT, since it was used in clinical practice, and was the basis of informing the studied persons whether they had an AAA or not. With the experience obtained from study II the mean maximum diameter from US and CT was used to define an AAA in study IV, to reduce the diagnostic shortcomings of each method.

US examination was carried out with an Acuson 128/10 instrument with a linear 4-, 3.5- or 2.5 MHz transducer or a convex 5- or 3.5 MHz transducer. All examinations were performed by the same experienced radiologist. The subjects were fasted four hours before examination.

The CT-scans were carried out with a General Electric High Speed machine. Helical CT-scans were done with 10 mm slices at 7.5 mm increment (space) from the xiphoid process to the aortic bifurcation. No intravenous contrast was administered. The images were stored on an optical disc from which the readings were done afterwards on a workstation (Advantage Windows) by one radiologist, blinded to the US results.

The largest anteroposterior (AP), transverse (TR) and maximum (Max) diameters were measured using the outermost US reflection with the transducer parallel to the longitudinal axis of the vessel and the outermost CT brightness of the infrarenal aorta.

Statistics and Ethics

Statistical evaluation of the data was carried out with a computer software package (SPSS PC version 8.0–12.0).

Independent samples t-test was used for comparison of normally distributed data and Wilcoxon rank sum test (Mann-Whitney U test) was used for comparison of non-parametric data. Paired t-test and Wilcoxon signed-rank test were used for comparison of paired data. Fisher's Exact test was used for comparison of two proportions. McNemar's Chi-square test was used to analyze differences in diagnosing AAA between definitions, techniques and measuring sites in study I. Spearman's rank correlation coefficient was used to analyze the correlations between difference and aortic size and between difference and BMI in study II. Kendall's tau-b was used to measure associations of ranked variables in study IV. To estimate the odds ratio for factors in relation to AAA after adjustment for atherosclerosis, multivariate forward-stepwise logistic regression models were used with AAA, or no AAA, as a dichotomous dependent variable in study IV. A probabilistic sensitivity analysis was performed in study V. Adjustments for multiple comparisons

were made in study I, and a p value <0.001 was considered significant. A p value <0.05 was considered significant in study II – IV.

All participants gave their informed consent and the studies were approved by the Committee of Ethics of Umeå University.

RESULTS

Study I

Of the 555 individuals invited, 506 accepted to participate. One man had had aortic surgery for occlusive disease with the use of a prosthetic graft and was excluded, giving an attendance rate of 91%. One woman was excluded because of no visibility at US and not attending at CT evaluation, because of claustrophobia. The remaining 504 subjects (248 men and 256 women) had a median age of 70 years. Seven men and one woman had already had surgery for infrarenal AAA, two men because of rupture and the others for AAA larger than 50 mm. Successful imaging of the infrarenal aorta was achieved in 95.8% with US. Ninety-four persons were invited for a CT evaluation (21 because of no visibility, 63 because of an aortic diameter 28 mm or more and 10 performed initially to validate the US examinations). One woman in whom the aorta could not be visualized changed residency and one man with US measured diameter of 30 mm did not accept further examination. The attendance rate for the CT evaluation was 98%.

The mean maximum infrarenal aortic diameter measured by US was 24.6 mm (SD 6.2) and when excluding those with a maximum infrarenal aortic diameter ≥ 30 mm it was 23.3 mm (SD 3.1). *Figure 4.*

Prevalence of AAA in men

(Prevalence according to the four definitions, referred to in *table 6*, page 24).

1. Thirty-five men with AAA (defined as maximum infrarenal aortic diameter ≥ 30 mm) were identified at the US scanning. Together with those who had had surgery a male prevalence of 16.9 % (35+7/248) was found. One man with an AAA (30 mm) measured by US chose not to participate in the CT evaluation. Ten of those found to have a diameter of 30 mm or more with US could not be confirmed at CT (nine with a diameter of exactly 30 mm at US and in six of these the imaging was suboptimal due to obesity or excessive bowel gas) and three were found to have a diameter of 30 mm or more at CT but not at US.

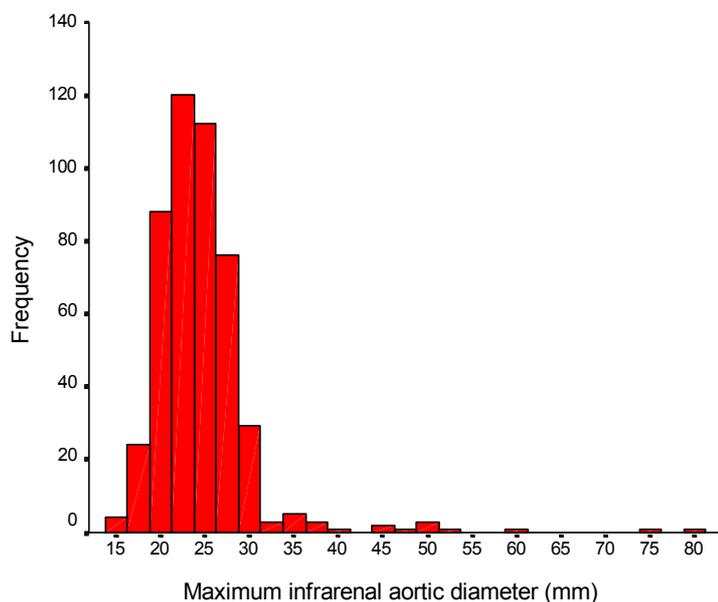


Figure 4. Distribution of US determined aortic diameter in 475 men and women.

2. Ten men with a maximum infrarenal aortic diameter exceeding at least 50% of the suprarenal aortic diameter were identified. The prevalence, including those who had had surgery, was 6.9 % (10+7/247). The largest aorta not found to be an AAA according to this definition was 43.0 mm (suprarenal diameter 29 mm). Of the subjects with aortas not defined as AAA according to this definition, but with a maximum infrarenal aortic diameter \geq 30 mm, three had a suprarenal diameter exceeding 30 mm.

3. A maximum infrarenal diameter of 40 mm or more, or an infrarenal diameter exceeding the suprarenal aortic diameter by at least 0.5 cm were identified in 19 men. Twelve had a diameter of at least 40 mm and one less than 30 mm (28 mm). In all subjects the infrarenal aortic diameter exceeded the suprarenal by at least 0.5 cm. When including those who had had surgery the prevalence was 10.5 % (19+7/247).

4. Using the definition of maximum diameter $\geq 1.5 \times$ normal infrarenal aortic diameter, predicted from a nomogram (Sonesson 1994) resulted in a male prevalence of 12.9% (25+7/248). All had a maximum infrarenal aortic diameter of 30 mm or more at US but eight men with a diameter of 30 mm or more did not meet this definition of an AAA (largest 31 mm). One man who had a diameter less than 30 mm at CT had an AAA according to this definition (29 mm).

There was a statistically significant difference (McNemar's Chi-square test) in diagnosing AAA between definition 2 and 1 and between definition 2

and 4 ($p < 0.001$). When adjusted for multiple comparisons no significant difference was found between definition 2 and 3 ($p = 0.002-0.008$). The latter definition differed significantly from definition 1. The differences between measuring site (maximum or anteroposterior diameter) and technique (US or CT) were not significant.

The prevalence was 12.5% among men age 65-69 years, and 22.0% among those 70-74 years. Thus, 70% of AAAs (defined as maximum infrarenal aortic diameter ≥ 30 mm by means of US) in men was found among those 70 years or older. The prevalence of large AAAs (≥ 50 mm) was 5.4% (95% CI 2.8–8.0) in men.

Table 7. Prevalence of AAA in men, according to different diagnostic criteria. Including seven men who had had surgery.

Definition	1				2		3		4	
	US		CT		Max	AP	Max	AP	US	
	Max	AP	Max	AP					Max	AP
Prevalence	16.9	16.1	14.2	13.8	6.9	6.5	10.5	10.1	12.9	12.9
95% CI	12-22	12-21	9.8-18	9.4-18	3.7-10	3.7-9.5	6.6-14	6.3-14	6.0-13	6.0-13
n	42	40	35	34	17	16	26	25	32	32

1. Infrarenal aortic diameter ≥ 30 mm
2. Infrarenal aortic diameter $\geq 1.5 \times$ suprarenal aortic diameter
3. Infrarenal aortic diameter ≥ 40 mm or exceed suprarenal aortic diameter by at least 0.5 cm
4. Infrarenal aortic diameter $\geq 1.5 \times$ normal infrarenal aortic diameter

Prevalence of AAA in women

1. In women eight AAAs (defined as maximum infrarenal aortic diameter ≥ 30 mm) were found at the US scanning. Together with the one who had had surgery the prevalence was 3.5% (8+1/256). Two of those found to have a diameter of 30 mm or more at US could not be confirmed at CT (in one there were difficulties to get a good imaging due to obesity or excessive bowel gas) and one was found to have a diameter of 30 mm or more at CT but not at US.

2. Two women were found to have a maximum infrarenal aortic diameter exceeding at least 50% of the suprarenal diameter. The female prevalence, including one who had had surgery, was 1.2% (2+1/256). The largest aorta found in women (infrarenal diameter 45 mm, suprarenal diameter 35 mm) was not an AAA according to this definition.

3. A maximum infrarenal diameter of 40 mm or more or infrarenal diameter exceeding suprarenal aortic diameter by at least 0.5 cm was seen in five women. Including the woman already operated on the prevalence was 2.3% (5+1/256).

4. If an AAA was defined as the maximum diameter $\geq 1.5 \times$ normal infrarenal aortic diameter 23 AAA were found at the US scanning, of these 15

were less than 30 mm (the smallest 24 mm). Since our criteria for the CT evaluation was an US measure of 28 mm or more, most of these subjects were never evaluated with CT. That gives a female prevalence of 9.4 % (23+1/256) for US.

There was a statistically significant difference (McNemar’s Chi-square test) in diagnosing AAA between the definition proposed by ISCVS/SVS Ad Hoc committee and the other definitions among women ($p < 0.001$). The differences between measuring sites (maximum or anteroposterior diameter) or techniques (US or CT) were not significant.

The prevalence was 2.6% among women age 65-69 years, and 4.8% among those 70-74 years. Thus, 67% of AAAs (defined as maximum infrarenal aortic diameter ≥ 30 mm by means of US) in women was found among those 70 years or older. The prevalence of large AAAs (≥ 50 mm) was 0.4% (0–1.2) in women.

Table 8. Prevalence of AAA in women, according to different diagnostic criteria. Including one woman who had had surgery.

Definition	1				2		3		4	
Technique	US		CT						US	
Diameter	Max	AP								
Prevalence	3.5	3.1	3.1	2.3	1.2	1.2	2.3	2.7	9.8	9.8
95% CI	2.0-6.3	1.7-5.8	1.7-5.8	1.2-4.8	0.5-3.1	0.5-3.1	1.2-4.8	1.5-5.3	6.9-14	6.9-14
n	9	8	8	6	3	3	6	7	25	25

1. Infrarenal aortic diameter ≥ 30 mm
2. Infrarenal aortic diameter ≥ 1.5 x suprarenal aortic diameter
3. Infrarenal aortic diameter ≥ 40 mm or exceed suprarenal aortic diameter by at least 0.5 cm
4. Infrarenal aortic diameter ≥ 1.5 x normal infrarenal aortic diameter

Comments

Based on the fact that all aneurysms with a diameter 50 mm or more met the criteria of the four definitions used those who had had surgery for AAA were included in the total prevalence regardless of definition. Furthermore all who were operated on had infrarenal reconstructions, the proximal neck was described as non-aneurysmatic and the suprarenal aorta was not considered to need replacement.

The radiologist was asked to make a note when there were some visibility problems. In 6.5% (in addition to the 4.2% with no visibility) there was some problem, due to excessive bowel gas or adiposity, and almost half of these were judged to have a diameter of 30 mm or more, which could not be confirmed at CT scan.

Study II

Difference between US and CT

In non-aneurysmal aortas (diameter <30 mm by means of CT) there was a significant difference between US- and CT-measured diameters ($p < 0.001$), while in AAAs the diameters did not differ significantly, *figure 5*. The difference was independent of the aortic size. Thus the proportional difference was larger for small aortas with a correlation coefficient of -0.38 ($p = 0.002$) for anteroposterior measurements.

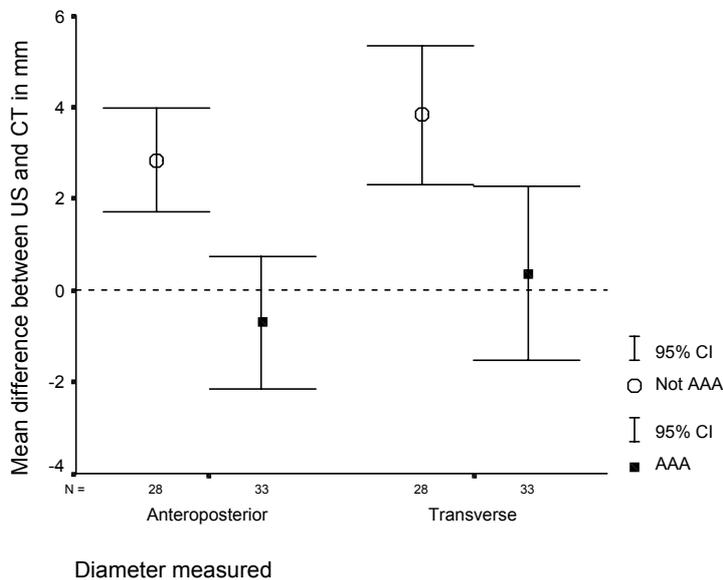


Figure 5. Mean difference and variability between US and CT.

Variability between US and CT

In non-aneurysmal aortas 95% of differences were expected to be less than 5.7 mm ($1.96 \times \text{SD}$) in anteroposterior measurements and less than 7.6 mm in transverse measurements. The CAD value (proportion of differences less than 5 mm) was 75% and 50% for anteroposterior- and transverse measurements respectively. In aneurysmal aortas 95% of differences were expected to be less than 8.0 mm in anteroposterior measurements and less than 10.6 mm in transverse measurements. The CAD value was 76% and 67% for anteroposterior- and transverse measurements respectively, *table 9*.

Table 9. US and CT agreement for different diameters.

	Anteroposterior	Transverse
Non aneurysmal aortas (28)		
Mean difference (SD)	2.8 mm (2.9)	3.8 mm (3.9)
95% limits of agreement	- 2.9 – 8.5 mm	-3.8 – 11.4 mm
CAD-value	75 %	50 %
Aneurysmal aortas (33)		
Mean difference (SD)	- 0.7 mm (4,1)	0.4 mm (5.4)
95% limits of agreement	- 8.7 – 7.3 mm	- 10.2 – 11.0 mm
CAD-value	76 %	67 %
All aortas (61)		
Mean difference (SD)	0.9 mm (4,0)	2.0 mm (5.0)
95% limits of agreement	- 6.9 – 8.7 mm	- 7.8 – 11.8
CAD-value	75 %	63 %

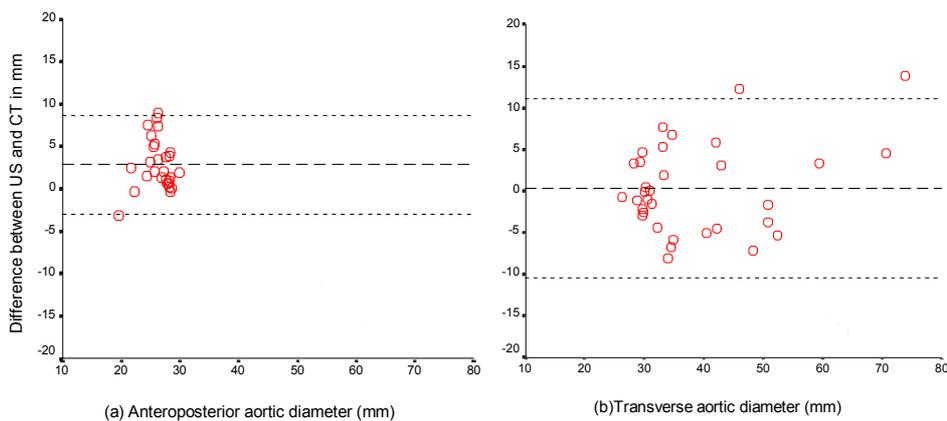


Figure 6. (a) difference and variability in anteroposterior diameter in non-aneurysmal aortas and (b) in transverse diameter in aneurysmal aortas

Figure 6 illustrates the systematic difference and low variability in anteroposterior diameter in non-aneurysmal aortas compared to no bias and high variability in transverse diameter in aneurysmal aortas.

Comments

The lack of agreement between US and CT was seen despite the fact that subjects with suboptimal visibility with US were excluded. Thus, all US-examinations included in this paper were considered to be of high quality.

When the differences in size between the two techniques were divided and analysed as two subgroups (AAA and non-AAA), a significant difference was observed in non-AAA but not in AAAs. Thus, one could suspect that the smaller the aorta the larger the differences and, vice versa, the larger the aorta the smaller the differences. However, when the same data were analyzed in a different way (correlation between differences and aortic size) no such differences were observed. As with any data-set, when dividing into subgroups, the criteria that define these groups will influence the results. The dividing line of 30 mm determined by means of CT is not a natural biological distinction, but was considered clinically relevant.

Study III

QoL effects related to screening

Twenty-four of the 27 patients with screening detected AAA (89%) and 45 of 59 individuals with normal aortas (76%) completed all questionnaires.

No significant differences in scale score were found between the AAA- and control groups before or after screening.

Within the AAA-group significant decreases were seen after screening in three SF-36 scales; *Physical Functioning*, *Social Functioning* and *Mental Health*; and in *Mental Health Cluster*. No decrease was observed within the control group (*table 2*).

Compared to 95% CI for the norms for the general Swedish population age 65–74 years there were no differences before screening but a lower mean score in all scales except for *Bodily Pain* and *General Health* 12 months after screening in the AAA-group. No such differences were seen for any scale in the control group, *table 10*.

The decrease in *Mental Health Cluster* score within the AAA-group was entirely due to six patients with low baseline scale score, *i.e.* a scale score within the 25th percentile in at least four scales, *Figure 7*. They did not differ from those with normal baseline score regarding age, sex or AAA-diameter. Within the control group no decrease in *Mental Health Cluster* score was observed in ten persons with low baseline scale score.

Table 10. Norms for the general Swedish population age 64 – 74 years and mean scale score for the AAA- and control group before and 12-months after screening

SF-36 scale *	Norms (95% CI)	Mean score in AAA-group			Mean score in control group		
		before screening	after screening	P **	before screening	after screening	P **
PF	72.5 (70.9 – 74.2)	73	68 ***	0.033	81	76	0.54
RP	65.3 (62.5 – 68.0)	65	62 ***	0.80	66	68	0.51
BP	69.2 (67.4 – 71.0)	68	73	0.083	65	68	0.48
GH	66.0 (64.4 – 67.6)	69	66	0.091	65	68	0.085
V	69.1 (67.4 – 70.7)	68	64 ***	0.081	69	70	0.57
SF	86.5 (85.0 – 88.0)	89	82 ***	0.046	88	88	1.00
RE	77.4 (74.9 – 79.8)	69	69 ***	1.00	71	76	0.26
MH	81.3 (79.9 – 82.7)	86	79 ***	0.019	82	83	0.69
PHC	not available	43	43	0.67	46	44	0.91
MHC	not available	52	49	0.029	51	52	0.27

* SF-36 scales and clusters according to table 1, page 21.

** difference within each group, using Wilcoxon signed-rank test.

*** difference compared to 95% CI of norms for the general Swedish population at same age.

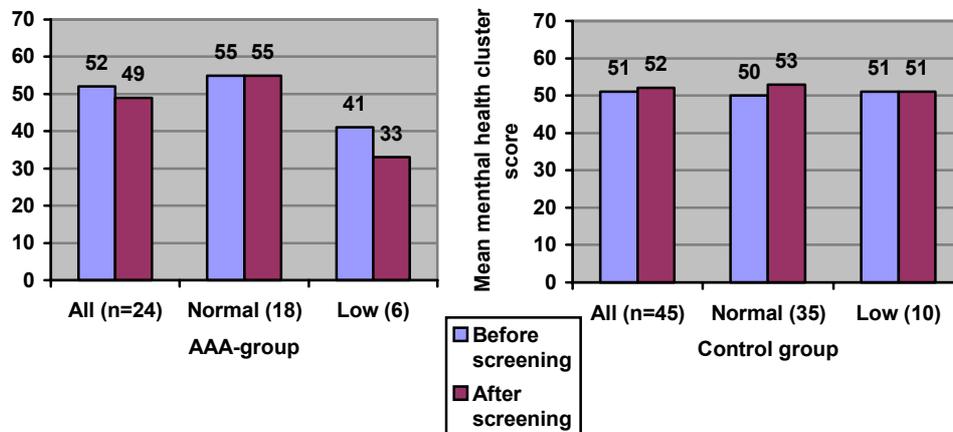


Figure 7. Mean mental health cluster (MHC) score before and one year after screening in 24 patients with screening-detected AAA and 45 individuals with normal aortic diameter. All = the whole group, Normal = subjects with normal baseline scale score in five scales or more, Low = subjects with low baseline score in at least four scales. A low baseline score was defined as a score within the 25th percentile in at least four of the eight scales before screening.

Comments

With an attendance rate in the screening population of 91 %, and of the AAA-patients and controls invited to the QoL-study of 89% and 76% respectively, the selection bias was limited. The main weakness of this study is the small size. The sample size needed per group to detect a 20-point difference between two experimental groups (two independent groups of observations) has been calculated to 14–47 for the eight scales, compared to 8–24 when differences between a group mean and a fixed norm or 6–19 when differences over time within one group are measured (two groups of paired observations) (Sullivan 1994). This difference in required sample size could explain why the AAA-group did not differ from the control group, whereas a difference was seen within the AAA-group and between scale score mean and the norm for a general Swedish population of the same age after screening in the AAA-group but not in the control group. Comparisons of repeated measures within groups permit a powerful matched statistical method. Thus, type II statistical error could be avoided when the differences between QoL before and after screening were evaluated.

The risk for a Type I error is obvious with multiple outcome measures, as in this study. In average every 20th comparison will falsely turn out significant due to chance alone with a cut-off level for significance at 5% and the risk to get a false significant result with ten measures is 40%. Although eight scales were used to measure QoL, they form two clusters, which were the main outcome. Furthermore, the study was considered to be hypothesis generating or explorative and therefore it was important to avoid a type II error.

The sub-analysis, of the effect of different baseline QoL, was not anticipated in the study design, but was conducted to explore the observed significant decrease in *Mental Health Cluster* score in the AAA-group. A similar observation was seen in AAA patients with a decrease of 10% or more in *Mental Health Cluster* score after screening, who had a significantly lower score before screening in almost all SF-36 scales and clusters (*table 3, study III, page 19*)

Study IV

Factors associated with AAA

The prevalence of AAA detected at screening was 12% (95% CI, 6–16) in men and 2% (0–4) in women ($p < 0.001$), when eight patients already operated on for AAA were excluded. Of 35 AAAs detected, 29 were found in men (83%, 95% CI 70–96). The odds ratio (OR) for male sex was 5.5 (2.3–13.8) and for female sex 0.2 (0.1–0.4). Age was associated with AAA in

men, where 74% of all AAAs were found in the older half of the population, OR 1.2 (1.1–1.4) per year. The prevalence was 17% (10–24) in men aged 70–74 years and 6% (1–10) in men aged 65–69 years ($p=0.009$). In women the corresponding proportions were 3% (0–6) and 2% (0–4) ($p=0.50$).

A reported history of CVD ($p=0.008$), CHD ($p=0.045$) and hypertension ($p=0.036$) were associated with AAA, as well as having had any atherosclerotic disease (58% v/s 26%, $p=0.001$) but not PAOD nor diabetes ($p=0.12$ and $p=0.77$).

There were more current smokers (23% v/s 9%, $p=0.034$) and smoke years (0.016) in the AAA group, while no differences were seen in the number who had ever smoked ($p=0.34$) or pack-years ($p=0.28$).

Significantly higher historical creatinine- ($p=0.026$), HDL- ($p=0.049$), LDL- ($p=0.001$), total cholesterol- ($p=0.001$) and TG levels ($p=0.035$) were found in the AAA group compared to controls, and the average weight at 60 years was higher for AAA patients ($p=0.020$). No differences were observed in blood pressure 11.6 years (mean time) before AAA-screening ($p=0.33$ – 0.62).

At AAA-screening (cross-sectional data obtained at age 65–75 years), the levels of creatinine, hsCRP and TG were significantly higher and the HDL concentrations were significantly lower in the AAA group ($p=0.021$, $p=0.003$, $p<0.001$ and $p=0.002$ respectively). No differences were seen for total cholesterol, LDL or Lp(a).

Several variables changed over time. However, only the change in hsCRP differed between the two groups ($p=0.015$), where a significant increase within the AAA group (+2.5 mg/l, $p=0.039$) but a slightly decrease within the control group (-0.1 mg/l, $p=0.002$) was observed. There was a significant decrease in LDL within the AAA group ($p=0.005$) but not within the control group ($p=0.11$), and a significant decrease in TG within the control group ($p=0.003$) but not within the AAA group ($p=0.60$).

A positive family history of AAA was reported in 6% (4–9) of the total investigated population. The difference in frequency of reported positive family history, prior to screening, between the AAA- and control groups did not reach statistical significance ($p=0.086$). However, two pairs of brothers with large AAAs were detected at screening. Thus, the prevalence of positive family history of AAA corrected after the AAA-screening was higher and significantly associated with AAA (29% v/s 7% $p=0.001$). The prevalence of AAA, among those with a first-degree relative with an AAA, was 30%. In men the corresponding frequency was 50% (24–76). Thirty-two percent (14–51) of all men with an AAA had a first-degree relative with an AAA, resulting in an odds ratio of 6.0 (2.0–18.0). The mean AAA diameter was 46 mm (36–56), among those with screening detected AAAs with a first degree relative with AAA compared to 38 mm (34–42) in those with a negative family history ($p=0.067$).

Interactions between factors associated with AAA

A history of atherosclerotic disease was significantly associated with male sex, hypertension, low HDL-levels, high TG-levels and elevated historical LDL-levels. For example, 37% of all men reported a history of atherosclerotic disease compared to 19% of all women ($p < 0.001$), and 61% of those reporting a history of atherosclerotic disease also reported a history of hypertension compared to 34% of those with no history of atherosclerotic disease ($p = 0.002$). There was also an association between smoking and hsCRP, where current smokers had a mean hsCRP of 5.3 mg/L compared to 2.6 mg/L for non smokers ($p = 0.023$) at screening.

After adjustment for atherosclerosis in a logistic regression model, current smoking and smoke years, historical LDL-, total cholesterol- and TG level as well as HDL-, TG- and hsCRP level at screening and having a first degree relative with AAA were independently associated with AAA. While hypertension, weight, creatinine level and historical HDL level were not, *table 11*. HsCRP retained the associations with AAA in a logistic regression model after adjustment for smoking ($p = 0.029$).

Table 11. Adjusted odds ratio* for factors associated with AAA.

Covariates	Odds ratio	95% CI	p
Any atherosclerotic disease	3.82	1.72 – 8.49	0.001
Hypertension	1.94	0.85 – 4.46	0.12
Current smoker	5.18	1.60 – 16.84	0.006
Smoke-years	1.02 / year	1.00 – 1.04	0.035
Weight (kg)	1.02 / kg	0.99 – 1.05	0.19
Historical HDL (mmol/l)	0.29 / mmol/l	0.07 – 1.22	0.092
Historical LDL (mmol/l)	2.32 / mmol/l	1.23 – 4.36	0.009
Historical Cholesterol (mmol/l)	1.90 / mmol/l	1.27 – 2.83	0.002
Historical TG (mmol/l)	1.91 / mmol/l	1.18 – 3.09	0.008
Creatinine ($\mu\text{mol/l}$)	1.02 / $\mu\text{mol/l}$	1.00 – 1.04	0.053
HDL (mmol/l)	0.11 / mmol/l	0.02 – 0.69	0.018
TG (mmol/l)	3.39 / mmol/l	1.76 – 6.52	< 0.001
hsCRP (mg/l)	1.10 / mg/l	1.01 – 1.19	0.025
First degree relative with AAA	4.37	1.47 – 12.97	0.008

* Adjusted for atherosclerosis with AAA (or no AAA) as the dependent variable. Based on sex- and age-matched data in a logistic regression model, using forward stepwise selection method (Likelihood ratio).

Fifty-nine per-cent of the investigated male population reported either a history of atherosclerotic disease, had ever smoked or had a positive family history of AAA. The risk of having an AAA was significantly associated with the number of these factors present, ($p < 0.001$, Kendall Tau-B), *table 12*. Ninety percent (95% CI 73–98) of all men with a screening detected

AAA reported at least one of these risk factors and in this group of men the prevalence of AAA was 18% (95% CI 12–25).

When either a history of atherosclerotic disease or a positive family history of AAA was present, the odds ratios were 2.8 and 2.9 respectively, compared to 19.6 when both were present, table 13.

Table 12. Interactions of three major factors (history of cardiovascular disease, ever smoked and having a 1st degree relative with AAA) associated with AAA in all 242 men.

Number of factors present	N	No. with AAA	Prevalence (95% CI)*	Odds ratio (95% CI)
0	101	4	4% (0-8)	1,0
1	89	11	12% (5-19)	3.4 (1.1-11.2)
2	45	10	22% (10-35)	6.9 (2.0 – 23.5)
3	7	4	57% (8-100)	32.3 (5.3-195.6)

* (p<0.001, Kendall Tau-B)

Table 13. Interactions between history of cardiovascular disease and having a 1st degree relative with AAA in 35 patients with AAA and 140 age- and sex matched controls.

History of cardiovascular disease	1 st degree relative with AAA	N	No. with AAA	Odds ratio (95% CI)	p-value
No	No	117	14	1,0	
Yes	No	40	11	2.8 (1.1 – 6.8)	0.026
No	Yes	7	2	2.9 (0.5 – 16.6)	0.22
Yes	Yes	11	8	19.6 (4.6 – 82.8)	<0.001

* Fisher's exact test

Comments

Selection bias was minimized by the population-based design and by the high attendance rate (91%). Case definition and risk of misclassification is determined by the accuracy of the AAA definition and the diagnostic technique used, and is discussed in detail in the general discussion section.

The main weakness is the small size, with only 35 cases. However, despite this low power, several significant associations were found. We did not correct for multiple comparisons in the statistical analyses, since the study design was hypothesis generating.

Although the historical data were collected prospectively, the study is not a true cohort study, since no information on the presence of AAA was available of the original cohort that entered the VIP-survey. The design, however, made it possible to analyse changes over time, which is novel.

Since surgery for AAA is a major event that may influence most of the factors that were studied and due to the risk for detection bias, the eight pa-

tients already operated on for AAA were excluded. Among those, two had a first-degree relative with an AAA (25%), all had CHD, none had diabetes and two were current smokers. Two were operated on before the VIP-survey and six were operated on after the VIP-survey but before the AAA-screening. No significant changes in results were observed if these six were included in the evaluation of the historical data.

Study V

Cost-effectiveness of screening for AAA

In base case (screening men at 65-years), the mean remaining life expectancies in the invited and non-invited groups was 16.0 and 15.9 years, respectively, and the cost per LYG was estimated to \$10 474. The mean remaining life expectancies in persons with AAA was estimated to 11.1 years if screened and 10.5 years if not screened.

In the non-invited group, 6.3/1000 persons had surgery for non-ruptured AAA and 10.4/1000 persons had ruptured AAA. In the invited group the corresponding proportions were 15.8 and 4.9 per 1000 persons. Thus, a 53% reduction in rupture incidence was observed.

The AAA related death incidence was 0.4% and 0.8% for the invited and non-invited group respectively, over the whole observation time, which corresponds to a 50% reduction. The cost-effectiveness of different screening strategies are presented in *table 14*.

Sensitivity analyses showed that the probability of fitting the criteria for elective surgery, the probability of rupture in the screened and non-screened groups and long-term survival were the most important parameters for the cost-effectiveness. The analyses also showed that the cost-effectiveness was rather insensitive to variations in the cost of screening and surgery and that the attendance rate had little impact on the cost-effectiveness ratio, *table 4, study V, page 32*.

Assuming general population utility in all health states resulted in a cost per QALY gained of \$13 900 for the base case strategy, which is slightly higher than the corresponding cost per LYG. A 10% reduction in utility all subsequent years after AAA surgery resulted in a cost per QALY gained of \$19 600, while assuming a 5% reduction in utility for worrying about the screening detected AAA resulted in cost per QALY gained of \$75 100.

Table 14. Cost-effectiveness of different screening strategies, compared to no invitation to screening

Screening strategy	Difference in life years per person	Cost per life year gained (\$)
65-year-olds with popliteal aneurysm*	0.182	8 309
65-year-olds with popliteal aneurysm	0.156	9 148
65-year-old siblings	0.068	8 761
65-year-olds with angina or claudication	0.031	10 392
60-year-olds with angina or claudication	0.029	9 841
65-year-old smokers	0.029	10 695
60-year-old smokers	0.026	10 203
60-year-olds with re-screening after 5 years	0.025	11 648
60-year-olds with re-screening after 10 years	0.023	12 168
65-year-olds with re-screening after 5 years	0.023	11 946
65-year-olds (base case)	0.020	10 474
60-year-olds	0.018	11 100
70-year-olds	0.014	14 084

* assuming base case population mortality

Critical areas where more information is needed

Factors needing better characterization are the natural course of AAA detected by re-screening and the age-specific natural course of the disease. Also QoL effects related to screening in terms of QALY needs to be better evaluated.

Comments

In the MASS study, approximately 0.2% and 0.4% of the patients in the screening and control groups had ruptured AAA and 1% and 0.3%, respectively underwent elective AAA surgery, after 4-years follow-up (Ashton 2002). The corresponding 4-year estimates from our model were 0.23% and 0.37% for AAA rupture and 0.72% and 0.26% for elective AAA surgery.

The MASS study found a difference of 0.14 deaths per 100 persons after 4 years and the Chichester study found a difference in AAA mortality of 0.21 deaths per 100 persons after 10 years (Ashton 2002, Vardulaki 2002). Our model estimated the mortality differences to be 0.10 deaths per 100 persons after 4 years and 0.23 deaths per 100 persons after 10 years. The cumulative AAA-related mortality for the two strategies is displayed in *figure 8*.

In a large population-based necropsy study, Bengtsson et al found that 13% of all AAA eventually rupture (Bengtsson 1992). The corresponding proportion was 11% in this paper. The surgery-rate of 3.9% per year and the

rupture-rate of 0.8% per year used in our model correspond well to the findings of the UK small Aneurysm Trial (The UK Small Aneurysm Trial 1998) and of the ADAM-study (Lederle 2000), where 3.6% were operated on each year and the rupture-rate were 0.7% per year, provided that 70% of all detected AAAs are less than 4.0 cm (Scott 1994, Lederle 2000, Paper I, Ashton 2002, McCarthy 2003).

The fact that the outcomes from the simulation model showed good agreement with those of large clinical studies was expected, since data from those studies in the form of a systematic review of the literature was the basis of the model. The stability of the results was tested with various sensitivity analyses and confirmed that the results were stable. The advantage of creating a model is that valid data from different studies, with heterogeneous study designs, can be entered into the model and that alternative strategies can be assessed in an environment that resembles a meta-analysis.

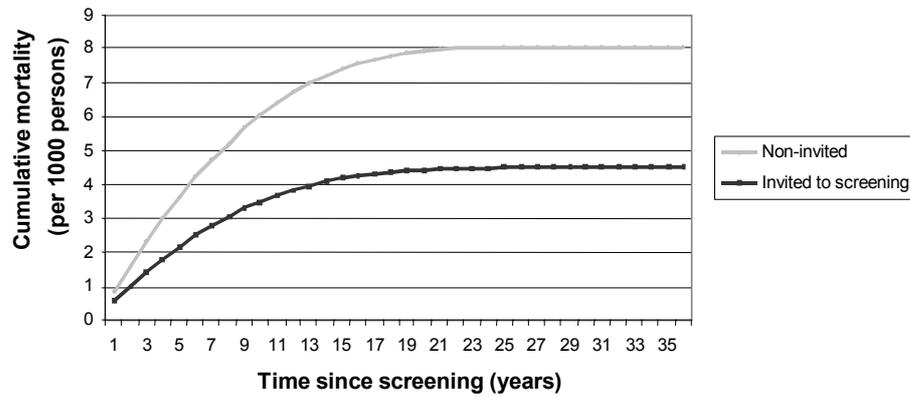


Figure 8. AAA-related mortality over time for 65-year old men invited to screening and those not invited.

GENERAL DISCUSSION

Methodological aspects on AAA epidemiology

Definition of AAA

The most striking weakness, concerning epidemiological studies on AAA, is the lack of a uniform definition of the disease. This is not a problem in most clinical situations but is a major problem in scientific projects. Most AAAs found at screening are small, and the dividing line between an AAA and a healthy aorta is of great importance and may significantly influence the outcome of the study.

The most accepted definition, of those displayed in *table 6*, defines an AAA as the maximum infrarenal aortic diameter being 30 mm or more (McGregor 1975). Being widely used there are several studies to compare with if this definition is chosen, and there is no need to define the individuals according to age, sex and BSA in order to calculate the normal aortic diameter. That is the case, however, when using the definition proposed by the ISCVS/SVS Ad Hoc Committee (Johnston 1991), where an AAA is defined as the maximum infrarenal aortic diameter being at least 1.5 times larger than the expected normal infrarenal aortic diameter. No prevalence study based on this definition has been published. An interesting finding in **study I** was that many women had an AAA with this definition (the smallest AAA had a diameter of only 24 mm). Several authors have clarified that the diameter of the abdominal aorta depends on age, sex and BSA (Pearce 1993, Sonesson 1994). Using the definition described by McGregor (McGregor 1975), a small 65-year old woman could have twice the aortic diameter expected and still not be classified as having an AAA. Some definitions relate the infrarenal aortic diameter to the suprarenal aortic diameter (Sterpetti 1987, Collin 1988, Moher 1992). In **study I**, the lowest prevalence was found using Sterpetti's definition (Sterpetti 1987) and rather large infrarenal aortas were considered non-aneurysmatic (for example one man with 43 mm and one woman with 45 mm). Collin's definition (Collin 1988) is seldom used but one definition that is found in the literature is a mixture of McGregor's and Collin's, an AAA is defined as the maximum infrarenal

aortic diameter being 30 mm (sometimes 35 mm) or more or a bulging of the infrarenal aorta (Bengtsson 1991). This definition is inexact and makes comparisons impossible.

Study I demonstrated how various definitions strongly influence the reported prevalence of AAA, confirming the finding of Moher et al (Moher 1994). The lack of a uniform definition makes it difficult to compare results between studies.

It should be noted that other aspects of the disease, for example pathophysiological aspects such as the expansion pattern, is not included in any of the proposed definitions. Misclassification is a possible source of error in studies of the natural course of small AAAs. It is notable that some very small AAAs, between 30 and 35 mm, do not expand at all (Nevitt 1989, Vardulaki 1998, Lindholt 2000, McCarthy 2003) and it is questionable whether these represent true AAA disease. The proportion of AAA not expanding at all increases as the diameter decreases.

Small AAA may not always represent true disease and could obscure or dilute the effect of true AAAs in risk factor studies. In the ADAM-study, the associations between various factors, such as smoking and cholesterol levels, and AAA were investigated. In order to avoid this possible bias, AAAs with a diameter of 3.0-3.9 and >4.0 cm were analyzed separately. The differences were small and the investigators concluded that using a diameter of 30 mm or larger as a cut-off point to define AAA, would not result in significant errors (Lederle 2000). However, more than 120.000 subjects were included in the ADAM-study, the largest population-based study ever, and bias due to misclassification may have an impact on the results from smaller studies.

The ability to compare the result with other studies was the rationale to use the definition proposed by McGregor in **study II** and **study IV**. The same definition was used in **study III**, based on clinical practice, and on what basis the studied persons were informed whether they had an AAA or not. The definition may have influenced the result in **study IV** and **study V**. Since **study V** was based on a systematic review of the literature, the definition proposed by McGregor was an obvious choice. The influence of the definition was less important in **study III**.

The desirable definition should be highly sensitive (*i.e.* have a high probability of classifying sick individuals as being sick) and specific (have a high probability of classifying healthy individuals as healthy). Unfortunately, there is often a trade-off between these two qualities. For a potential life-threatening but treatable condition, such as AAA, a definition with high sensitivity is important. The most accepted definition, defining an AAA as the maximum infrarenal aortic diameter being 30 mm or more, fulfills this prerequisite. For women, it may be more appropriate to relate the diameter to the expected normal diameter or to use a lower cut-off diameter. However, adopting such wide criteria increases the risk to define false-positive subjects as having AAA. A more specific definition may confirm or rule-out a diagnosis that has been suggested by other less specific criteria. In order to dem-

onstrate a true widening of the aorta the relation between infrarenal- and suprarenal diameter must be assessed. Furthermore, to demonstrate an expansion of a potential AAA, a follow-up period with repeated assessments is required. Thus, a fix diameter, for example 30 mm, may not be a proper definition of AAA, but an excellent cut-off level for further assessment and/or follow-up. A prospective study where the diameter, the ratio of infrarenal to suprarenal diameter and the expansion pattern are evaluated may improve the predictive value of any future definition.

Diagnostic techniques

The suprarenal aorta is always well visualized by CT but not by US (Gomes 1978, Ellis 1991). The origin of at least one renal artery was seen in only 11% of the subjects investigated by Gomes and co-workers (Gomes 1987). Visibility of the entire infrarenal aorta by means of US may be impossible in obese persons and in subjects with excessive bowel gas or periaortic disease. The reported visibility of the infrarenal aorta in previous US studies is 97.3 – 99.9% (Bengtsson 1991, Scott 1991, Smith 1993, Lederle 1997, Boll 1998) but is not reported in most publications (Bengtsson 1989, Nevelsteen 1991, Bengtsson 1992, Adams 1993, van Laarhoven 1993, McSweeney 1993, Morris 1994, Sowter 1994, Eisenberg 1995, Simoni 1995, Jaakkola 1996, Lindholt 1997, Pleumeeker 1999). In **study I** the visibility for US was lower, 95.8%. This outcome may have been a consequence of the study design. The investigator was experienced with ultrasound and had access to modern US technique. He knew, however, that if there was even a small doubt, a CT-examination could be requested. The study design of **Study I** is unique for a population-based study on the prevalence of AAA. Visibility with ultrasound is a continuous variable and in previous studies lower grades of visibility problems may have been neglected. In **study I**, with the combination of US and CT, adequate information on the diameter of the aorta was obtained in 99.4%.

Decisions and conclusions in clinical and scientific situations are based on the aortic diameter and its changes over time. A size difference of a few mm may influence surgical decision-making. Therefore, the precision of the measurement and the awareness of its shortcomings are important.

For US the reported interobserver variability is 2.2 – 7.5 mm in AP diameters and 2.8 – 15.5 mm in transverse diameters (Bengtsson 1989, Ellis 1991, Akkersdijk 1994, Lederle 1995, Jaakkola 1996, Singh 1998). The reported interobserver variability for CT is 2.8 – 4.3 mm for AP diameters (Lederle 1995, Jaakkola 1996, Aarts 1999, Singh 2003). Jaakkola *et al* found a mean interobserver variability of 7.0 mm for transverse diameters in aneurysmal aortas (Jaakkola 1996). Aarts *et al* demonstrated that the observed variability decreased when going from hard copy to workstation (Aarts 1999).

The agreement between US and CT has been evaluated in previous studies (Gomes 1987, Ellis 1991, Thomas 1994, Lederle 1995, Jaakkola 1996, Sprouse 2004, Singh 2004), *Table 15*. The finding in **study II**, that US overestimates the diameter compared to CT, is consistent with that reported by Ellis *et al* (Ellis 1991). In that same study the proportional difference was larger for small aortas, as seen in **study II**. Others have found US diameters to be smaller compared with CT (Thomas 1994, Lederle 1995, Jaakkola 1996, Sprouse 2004) while Grimshaw *et al* (Grimshaw 1992) found no consistent bias between the measurements. The observed difference in mean diameter in **study II** was, however, confined to subjects with non-aneurysmal aortas, while no difference in mean diameter was found in subjects with aneurysmal aortas.

Table 15. Studies on comparison between US and CT measurements of maximal infrarenal aortic diameter.

Study	N	Mean difference (mm) *	SD	95% limits of agreement	Difference		
					2 mm or less	5 mm or more	10 mm or more
Studies with and without aneurysms							
Jaakkola	33	- 2.1	-	-	54 %	16 %	-
Singh #	555	-1.0	3.2	-7.2 – 5.2	62%	14%	6%
Thomas	36	- 4.4	3.2	- 10.7 – 1.9	-	-	-
Study II	61	+ 0.9	4.0	- 7.1 – 8.9	44 %	25 %	0%
Studies with aneurysms							
Jaakkola	19	- 2.6	3.9	- 10.4 – 5.2	48 %	26 %	-
Grimshaw	20	- 0.1	1.8	- 3.5 – 3.4	-	-	-
Lederle	258	- 2.7	4.9	- 12.4 – 7.0	44 %	33 %	-
Ellis	10	+ 0.1-3.1	-	-	-	-	-
Gomes	28	- 1.0	-	-	-	-	57 %
Singh #	334	-0.3	3.5	-7.3 – 6.6	62%	14%	1%
Sprouse	38	-4.1	-	-2.6 – 11.0	-	-	-
Study II	33	- 0.7	4.1	- 8.8 – 7.5	42 %	24 %	0%
Studies without aneurysms							
Jaakkola	14	- 1.5	2.1	- 6.2 – 2.0	61 %	5 %	-
Singh #	221	-1.9	2.2	-6.2 – 2.3	62%	13%	0%
Study II	28	+ 2.8	2.9	- 2.9 – 8.5	46 %	25 %	0%

* Difference = US – CT

AP plane

The finding in **study II**, that the variability between the two techniques was larger in aneurysmal than in non-aneurysmal aortas is supported by Jaakkola *et al* and the Tromsø study (Jaakkola 1996, Singh 2004) while no such difference was observed by Thomas *et al* (Thomas 1994). In **study II**, transverse measurements had a larger variability than anteroposterior, an observation also reported by Ellis *et al* (Ellis 1991).

Vessel angulation has been suggested to explain some of the observed disagreement between the two techniques (Lederle 1995). The US examiner may correct for this by adjusting the probe to maintain a view of the aorta perpendicular to the blood flow. Traditional axial-CT lacks this ability, and the diameter may be represented by an oblique measurement instead of a more accurate cross-sectional measurement (Kritpracha 2002). In a recent publication by Sprouse and co-workers CT became unreliable when aortic angulation was greater than 25° (Sprouse 2004)

The question of whether or not screening programs for AAA are worthwhile is controversial. One of the prerequisites is to have access to a reliable diagnostic method (WHO-criteria, page X). In **study I**, both US and CT were used in diagnosing AAA. When an AAA was defined as a maximum infrarenal anteroposterior diameter of 30 mm or more, the prevalence in men aged 65 – 75 years was 16.1% by means of US compared to 14.2% when CT was the diagnostic method. The difference in prevalence was not significant, but several patients with an AAA on US became "healthy", if the results of CT were relied upon.

How should we apply this information into clinical or scientific practice? It seems as if systematic difference (bias) is conditioned locally and should therefore be assessed regularly, to facilitate the decision-making process. The observed lack of agreement between the two techniques was the rationale for the diagnostic criteria used in **study IV**, where the mean maximum diameter from US and CT was used to define an AAA.

The variability between US and CT, seen in transverse measurements was unacceptable in **study II** (a SD as high as 5.4 in aneurysmal aortas and a CAD-value of only 50% in non-aneurysmal aortas). Therefore, measuring the anteroposterior diameter is preferred, although only a difference of 8 mm or more is likely to signify a real difference. Holdsworth *et al* showed that an elliptical cross-section is common and introduced the concept of “mean cross-sectional area” as basis for AAA measurement (Holdsworth 2004). Measuring aneurysm volume instead of diameter may further reduce variability.

A common clinical experience is suddenly rapid expanding aneurysms or aneurysms that expand very slowly, not at all or even seem to decrease in size. Whether this is a true expansion pattern or an expression of intraobserver-, interobserver- or intertechnique differences is unclear and should be assessed at the local institution. When assessing possible expansion of an AAA, the investigator should review previous examinations simultaneously and not base the decision on the results from previous measurements con-

ducted by another physician (Singh 2003). This may reduce the impact of interobserver variability. Based on the surveillance of 63 patients with fast growing AAA, Sharp and co-workers challenged the practice of rapid expansion as an indication for elective repair. They found that after a period of fast growth the rate of expansion reverts towards the population average, which in part may be an effect of measurement error (Sharp 2003).

In routine clinical practice a person with an aortic diameter of 25 mm is considered healthy, and a person with a diameter of 33 mm is informed of having a potentially lethal disease requiring yearly ultrasound surveillance. These two persons may, however, in fact have exactly the same aortic diameter. One quarter of our patients will have a difference greater 5 mm between US and CT measurements. Should we have a sparse surveillance on persons with an aortic diameter of 25-29 mm, performing a new US after three years, or should we maybe perform a CT to be able to inform the person if he is healthy or not?

Technical improvement may reduce the variability. Länne *et al* (Länne 1997) reported improved reliability of a newly developed echo-tracking ultrasonic system measuring the luminal interface, with an intra- and interobserver variability less than one mm. Computerized programs that produce three-dimensional CT reconstruction have recently been developed. As for US, the technique may compensate for vessel angulation. In the work by Sprouse and co-workers (Sprouse 2004) the variability between US and three-dimensional CT was low and insensitive to aortic angulation. The method is a strong candidate to become the “golden standard” in measuring the aortic diameter.

Sample selection

The populations examined might not be representative of the background population. Either the population sample is recruited in a nonrandomized way or the nonresponders may constitute a selected group with a different prevalence of AAA (Janzon 1986, Ögren 1996). A population-based- or multicentre design may improve the generalizability, while single centre studies are more prone to differences in case mix, selection and data enhancement, including publication bias (Campbell 1991, Zarins 1997, Michaels 2003).

The reported operative mortality varies considerably in the literature. A great part of this variability is related to methodological differences. Single-center reports often describe low 30-day perioperative mortality following elective repair, sometimes as low as 0% (Perry 1988). However, these data cannot be generalized to larger populations. A review of 14 recent population-based and multicentre studies in **study V**, found an average mortality rate of 5.3% (Wen 1996, Kazmers 1996, Koskas 1997, Norman 1998, The

UK Small Aneurysm Trial 1998, Semmens 1998, Galland 1998, Dardik 1999, Lawrence 1999, Heller 2000, Huber 2001, Ashton 2002, Lederle 2002).

A distinction should be made between outcome after elective repair and surgery for non-ruptured AAA. The latter include emergency operations due to various reasons, for example a tender non-ruptured AAA. Emergency operations have higher mortality than elective repair, which may influence the outcome. Furthermore, the term is not clearly defined and inhabits various subgroups. Thus, outcome reports on non-ruptured AAA surgery may be less sensitive to selection bias. Based on mortality reported during 1999-2003 (3 689 procedures) in the Swedish vascular database (Swedvasc) a 30-day mortality of 3.3% (95% CI: 2.8-3.9) was seen after surgery for non-ruptured AAA, compared to 2.7% (2.1-3.4%) after elective surgery for asymptomatic AAA (Swedvasc 2003). This difference was due to the fact that patients operated on for symptomatic non-ruptured AAA had a 30-day mortality of 3.4% and those operated on emergently for non-ruptured AAA had a mortality of 6.9%. The difference between the three groups was statistically significant ($p=0.002$, Kendall Tau-B).

In order to avoid selection bias the attendance rate should be high. The attendance rate in **study I** was 91% for the US screening and 98% for the CT evaluation, the highest ever reported. In previous studies the attendance rates have been approximately 75% and seldom above 80% (Collin 1988, Bengtsson 1991, Smith 1993, Holdsworth 1994, Morris 1994, Scott 1995, Simoni 1995, Ögren 1996, Grimshaw 1997, Lindholt 1997, Lederle 1997, Boll 1998, Vasquez 1998, Wilmink 1999, Jamrozik 2000, Kyriakides 2000, Newman 2001, Lederle 2002, MASS 2002, McCarthy 2003). The high attendance rate, observed in **study I**, is probably explained by the combination of previous experience of regular health examination within the VIP-study and the fact that ruptured AAA is a fairly common and well-known cause of *mors subita* in this particular population.

In outcome studies it is also important to report the proportion unfit for inclusion or intervention and lost to follow-up. In a review of nine studies on operative mortality in **study V**, 2 – 24% were reported unfit for surgery and an additional 3 - 8% refused surgery (Fielding 1981, Johansson 1990, Scott 1991, Scott 1995, UK small Aneurysm Trial 1995, Kyriakides 2000, Valentine 2000, Lindholt 2002, Vardulaki 2002). Thus, up to one third of those initially intended to treat may drop out.

In prevalence studies, most authors never report how they deal with those who already had had surgery for AAA (Collin 1988, Bengtsson 1989, Scott 1991, Nevelsteen 1991, Bengtsson 1992, Sowter 1994, Morris 1994, Simoni 1995, Eisenberg 1995, Lindholt 1997, Pleumecker 1999). A few exclude them (Bengtsson 1991, Adams 1993, McSweeney 1993, Lederle 1997, Boll 1998) and some include them (van Laarhoven 1993, Fitzgerald 1995, Jaakkola 1996) in prevalence estimates. Holdsworth *et al* refer to “the true incidence” when they are included (Holdsworth 1994). Whether they should be

included or not is an issue of importance because of the impact on prevalence. When dealing with the total prevalence in the population they should be included. In any case they should be reported.

Most of the AAAs found in **study I** were observed in the older age group. Since age-interval often varies between studies it is difficult to compare the results between them. If the prevalence is reported in 5- and 10-year intervals comparisons are facilitated. Due to the influence of age and sex on most outcomes, presentation of age- and sex- specific data is preferable.

Older studies may not be representative of the contemporary situation, since inclusion, performance and outcome have changed during the last decades (Darling 1980, Crawford 1981, Bickerstaff 1984, Chen 1997, Zarins 1997, Dardik 1998, Bradbury 1998, Semmens 1998).

Prevalence of AAA

General populations

The reported prevalence of AAA in elderly men varies from 2.7 to 8.8% in population-based US studies, *table 16* (Collin 1988, Bengtsson 1991, Smith 1993, Holdsworth 1994, Morris 1994, Scott 1995, Simoni 1995, Ögren 1996, Grimshaw 1997, Lindholt 1997, Lederle 1997, Boll 1998, Vasquez 1998, Wilmink 1999, Jamrozik 2000, Kyriakides 2000, Newman 2001, Lederle 2002, MASS 2002, McCarthy 2003). In these studies, with more than 200 000 subjects scanned, 9 000 AAA were found and the mean prevalence was 5.0%. This is, however, a very heterogeneous group, especially concerning the age of the participants, ranging from 50 to 83 years. Furthermore, the size of the ADAM-study gives it a large influence on the average prevalence. The frequency of large AAA with a diameter of more than 50 – 55 mm varies from 0.2 to 2.2%, *table 17*.

Most screening studies have investigated populations with broad age-intervals and few reports of the age-specific prevalence are available. Based on five screening studies on 65-year-old men the prevalence was estimated at 5.5% (SD 0.09%) in **study V** (Scott 1994, Vazquez 1998, Kyriakides 2000, Newman 2001, McCarthy 2003). Of these 7.7% were assumed to be 55 mm or more, corresponding to a prevalence of 0.42% of large AAA (Jamrozik 2000, MASS 2002, McCarthy 2003). The only valid data on the prevalence among younger men comes from the large autopsy study from Malmö, Sweden (Bengtsson 1992) and from the Huntingdon screening study in the UK (Vardulaki 1999, Wilmink 1999). Based on these studies the prevalence in men aged 60 years was estimated to 3.4% and at 70 years to 6.1% (**study V**).

Few studies have investigated the prevalence among women. A mean prevalence of 1.0% was seen in the published reports that included women (Scott 1995, Simoni 1995, Newman 2001, Lederle 2002). In **study I** the male:female ratio was 4.8:1, a finding confirmed by others (Scott 1995, Newman 2001, Lederle 2002). Thus, more than 75% of all AAA will be found in men >65 years, representing about 45% of the population at that age.

Table 16. AAA prevalence in population-based US screening studies.

Author	Setting	Attend. Rate (%)	Median age	N	Definition	Prevalence	
						Men	Women
Bengtsson	Sweden	75	74	364	≥ 30 mm	8.5	-
Boll	Netherl.	83	60-80	2 419	≥ 30 mm	8.1	-
Collin	UK	52	65-74	447	≥ 30 mm ^a	4.2	-
Holdsworth	UK	78,5	65-79	628	≥ 30 mm	6.7	-
Grimshaw	UK	76	60-75	10 061	≥ 30 mm	7.2	-
Jamrozik	Austral.	70.5	65-83	12 203	≥ 30 mm	7.2	-
Kyriakides	UK	72.5	65	3 497	≥ 30 mm	4.9	-
Lederle	USA	30	50-79	73 451	≥ 30 mm	4.7	1.3
Lindholt	Denm.	76	65-73	4 843	≥ 30 mm	4.0	-
MASS	UK	80	65-74	27 147	≥ 30 mm	4.9	-
McCarthy	UK	85	65	29 906	≥ 30 mm ^a	2.7	-
Morris	UK	75	65-79	1 061	≥ 30 mm ^a	8.8	-
Newman	USA	84	> 65	4 734	≥ 30 mm	7.3	1.7
Scott	UK	68	65-80	5 394	≥ 30 mm	7.6	1.3
Simoni	Italy	59	65-75	1 601	≥ 30 mm	8.8	0.6
Smith	UK	76	65-75	2 597	≥ 30 mm	8.4	-
Vazquez	Belgium	41	65-75	723	≥ 30 mm	4.5	-
Wilmink	UK	74	>50	9 729	≥ 30 mm	4.8	-
Ögren	Sweden	81	74	343	≥ 30 mm ^a	6.7	-
Study I	Sweden	91	65-75	505	≥ 30 mm	16.9 14.6 ^b	3.5 3.1 ^b

a. A different AAA definition was used in the original study. This frequency was calculated from the data in the paper.

b. Not including those operated on for AAA

Table 17. Prevalence of large AAA in population-based US screening studies

Author	Setting	Attend. Rate (%)	Median age	N	Definition	Prevalence	
						Men	Women
Bengtsson	Sweden	75	74-74	364	≥ 50 mm	2.2	-
Boll	Netherl.	83	60-80	2419	≥ 50 mm	1.7	-
Collin	UK	52	65-74	447	≥ 50 mm	0.4	-
Holdsworth	UK	78.5	65-79	628	≥ 50 mm	1.6	-
Jamrozik	Austral.	70.5	65-83	12203	≥ 50 mm	0.7	-
Jamrozik	Austral.	70.5	65-83	12203	≥ 55 mm	0.5	-
Lederle	USA	30	50-79	73 451	≥ 50 mm	0.5	-
Lederle	USA	30	50-79	73 451	≥ 55 mm	0.3	-
Lindholt	Denm.	76	65-73	4843	≥ 50 mm	0.5	-
MASS	UK	80	65-74	27147	≥ 55 mm	0.6	-
McCarthy	UK	85	65	29906	≥ 55 mm	<0.5	-
Scott	UK	59	65-80	4122	≥ 50 mm	1.0	0.2
Wilkinson	UK	74	>50	9729	≥ 50 mm	0.6	-
Ögren	Sweden	81	74-74	343	≥ 50 mm	2.0	-
Study I	Sweden	91	65-75	505	≥ 50 mm	4.8	0.4
						2.1 *	0 *

* Not including those operated on for AAA

High risk groups

AAA is known to be associated with atherosclerotic disease. Another known high-risk group is close relatives of AAA patients. Screening studies in such high-risk populations have revealed the highest prevalence estimates.

In a screening study of 147 men with claudication, Bengtsson *et al* found a prevalence of 8.2% (Bengtsson 1989). In a review of seven risk factor studies (**study V**), 10% of 65 years old men with claudication or angina pectoris were estimated to have an AAA (Smith 1993, Pleumeekers 1995, Kanagasabay 1996, Alcorn 1996, Jamrozik 2000)

Bengtsson (Bengtsson 1996) reviewed seven sibling studies where an AAA was defined as an aortic diameter of 30 mm or more. The mean age of both men and women was 64 years. The average prevalence was 18.6% (95% CI 13 – 24%) among men and 3.6% (1 – 6%) among women (Bengtsson 1989, Webster 1991, Adamsson 1992, Adams 1993, Moher 1994, Jaakkola 1995, Fitzgerald 1995). About 1.5% of all AAAs will be found in siblings to AAA patients, who represents about 0.5% of the population (Jamrozik 2000).

Smoking is a known risk factor for AAA. A review of seven risk factor studies in **study V** found that about 82% of men with an AAA reported a history of smoking and about 27% were current smokers. In average, 63% of

the total investigated male populations reported a history of smoking. The average frequency of current smoking was 15%. The prevalence of AAA among current smokers was estimated to 9.5% (Krohn 1992, Smith 1993, Pleumeekers 1995, Alcorn 1996, Simoni 1996, Jamrozik 2000, Vardulaki 2000). Similar prevalence estimates were observed in patients operated on for carotid artery stenosis (Bengtsson 1988) and in patients with myocardial infarction (Lindholt 1997).

In two studies patients with obstructive pulmonary disease (COPD) were found to have a high prevalence of AAA (van Laarhoven 1993, Lindholt 1997). This finding was not confirmed in the larger ADAM-study (Lederle 1997, Lederle 2002). The low attendance rate (30%) in the ADAM-study may have an impact on this finding; maybe patients with COPD are less likely to attend screening for AAA?

The Norsjö municipality

The prevalence found in the Norsjö municipality (**Study I**) is the highest ever reported in a general population, *table 16*. Depending on which study compared to, how the prevalence was calculated and which diagnostic technique was used, the prevalence found in the Norsjö municipality is 1.3 – 6.3 times higher for men and 2.0 – 5.8 times higher for women. When confidence intervals are compared, the prevalence found in **study I** is statistically significantly higher than that of any other report (Collin 1988, Bengtsson 1991, Smith 1993, Holdsworth 1994, Morris 1994, Scott 1995, Simoni 1995, Ögren 1996, Grimshaw 1997, Lederle 1997, Lindholt 1997, Vasquez 1998, Boll 1998, Wilmink 1999, Kyriakides 2000, Jamrozik 2000, Newman 2001, MASS 2002, McCarthy 2003).

The prevalence found in the Norsjö municipality (**study I**) is higher than, or identical to that reported from studies on high-risk populations, but in some of those studies the median age was lower. The total population of the Norsjö municipality could be considered as a high-risk population for AAA. Since the attendance rate was high and CT confirmed all AAAs, the prevalence estimate is reliable.

Risk factors for AAA

Atherosclerosis

Few prospective studies evaluating risk factors for AAA were published. In the Chicago Heart Association cohort (Rodin 2003), cholesterol, smoking and blood pressure in middle age were associated with the clinical diagnosis of AAA after 30 years of follow-up. Similar findings were reported from the

Honolulu Heart Program cohort (Reed 1992) during 20-year follow-up, while no association with cholesterol was seen in the Whitehall cohort (Strachan 1991). In these studies cases were identified from surgical reports or death certificates, making comparisons with screening-based studies questionable. Furthermore, interactions with atherosclerosis at older age were not assessed in these studies.

Only two prospective studies assessing risk factors to develop AAA based on screening detected AAA were published. In the Edinburgh Artery Study (Lee 1997), only smoking was significantly associated with AAA in 34 persons with screening detected AAA with risk factors assessed 5 years before screening. In the Cardiovascular Health Study (Alcorn 1996) there was a strong association of cardiovascular risk factors, including cholesterol, and AAA. However, risk factors were assessed only 1-4 years before screening and a different AAA-definition was used. In **study IV**, elevated LDL- and total cholesterol levels and TG levels at age 60 years were independently associated with screening detected AAA after a median of 12 years of follow-up.

The association between AAA and atherosclerosis observed in **study IV** is consistent with previous reports (Pleumeekers 1995, Simoni 1995, Alcorn 1996, Kanagasabay 1996, Lee 1997, Jamrozik 2000, Lederle 2000, Vardulaki 2000, Blanchard 2000, Singh 2001, Newman 2001, Rodin 2003). This relationship, however, is complex and may influence the interpretation of other associations found. The association of male sex with atherosclerosis and smoking may partly explain the higher prevalence of AAA seen in men. Furthermore, the association with hypertension, seen in **study IV**, was lost when the presence of atherosclerosis was included in the model. The absence of a relationship between treated hypertension and AAA is consistent with several previous studies (Lindholm 1985, Collin 1988, Bengtsson 1991, Scott 1991, Reed 1992, Smith 1993, Alcorn 1996, Lee 1997, Blann 1998, Blanchard 2000), whereas others found hypertension to be associated with AAA (Strachan 1991, Krohn 1992, Simoni 1995, Kanagasabay 1996, Jamrozik 2000, Vardulaki 2000, Törnwall 2001, Singh 2001, Rodin 2003). In the ADAM-study (Lederle 2000) hypertension was significantly associated with AAA, but only marginally so.

Although associated with atherosclerosis, lower HDL- and elevated TG levels remained independently associated with AAA in **study IV**, when atherosclerosis was added to the model. The literature is contradictory in this respect. In the ADAM study (Lederle 2000) high cholesterol levels were independently associated with AAA in a multivariate analysis including atherosclerosis. Simoni and co-workers found lower HDL levels and higher TG levels among 69 patients with screening-detected AAA compared to 1460 subjects found to have a normal aortic diameter, while no difference was observed in LDL- or total cholesterol levels (Simoni 1996). In the Tromsø study a strong inverse association with a dose-response relation was found between HDL levels and AAA (Singh 2001). In a population-based

screening study in Malmö, Sweden, Bengtsson *et al* found no difference in total cholesterol- or TG levels between subjects with or without an AAA (Bengtsson 1991). Within the Huntingdon screening programme, 206 men with screening detected AAA were found to have higher LDL levels than 252 age-matched male controls. They suggested that LDL might act via inflammatory mediated matrix degeneration (Hobbs 2003).

Lp(a) is considered a major and independent risk factor for cardiovascular disease (Angles-Cano 2001), partly by compromising fibrinolysis through its competition with plasminogen (Morrisett 2000). The lack of an association of Lp(a) levels and AAA in **study IV** is consistent with the report from a screening study in Italy (Simoni 1996). However, elevated Lp(a) levels associated with AAA have been reported in two studies on large AAAs (Papagrigrakis 1997, Schillinger 2002). One paper reported significantly elevated Lp(a) levels in 75 patients with AAA, identified from surgical reports, CT-angiography or death certificates, compared with 39 patients with thoracic aortic aneurysms and 43 healthy control subjects (Schillinger 2002). In a study from Umeå, a negative correlation was found between Lp(a) levels and elastin-derived peptides, indicating that Lp(a) inhibit elastolysis (Petersen 2003)

Arterial remodelling associated with atherogenesis was suggested to be linked with aneurysm development (Glagow 1987, Zarins 1988, Zarins 1990, Zarins 1992). Zarins and colleagues found aortic dilatation and aneurysm formation in monkeys with atherosclerosis after treatment with an atherosclerosis regression diet (Zarins 1990, Zarins 1992). In **study IV** the subjects who eleven years later developed AAA had significantly higher historical triglyceride, LDL- and total cholesterol levels compared to healthy controls. Furthermore, patients with AAA decreased their LDL levels significantly over time, controls did not. Total cholesterol- and Lp(a) levels decreased significantly among all studied persons ($p < 0.001$), and although this decrease was more pronounced among the AAA patients, the difference between groups was not significant. Although the results from **study IV** suggest that arterial remodelling offers an alternative explanation for the high prevalence of AAA in the Norsjö population, due to the small sample-size in this limited population, firm conclusions cannot be made.

Smoking

Smoking has consistently been associated with AAA in the literature (Strachan 1991, Pleumeekers 1995, Simoni 1995, Alcorn 1996, Kanagasabay 1996, Lee 1997, Naydeck 1999, Jamrozik 2000, Blanchard 2000, Lederle 2000, Vardulaki 2000, Törnwall 2001, Singh 2001, Rodin 2003) and several studies have found a dose-response relationship suggesting a causal role for smoking in the aetiology of AAA (Jamrozik 2000, Vardulaki 2000, Blanchard 2000, Singh 2001, Newman 2001).

The findings in **study IV** that current smoking and duration of smoking are the most important smoking variables associated with AAA are consistent with previous investigations (Krohn 1992, Jamrozik 2000, Vardulaki 2000, Singh 2001, Törnwall 2001). Compared to other population-based studies smoking was less frequent in the Norsjö municipality, only 9% of the population being current smokers (Krohn 1992, Pleumeekers 1995, Jamrozik 2000, Lederle 2000, Vardulaki 2000, Singh 2001, Rodin 2003).

The mechanism by which smoking may contribute to the development of AAA has not been clearly elucidated. Cigarette smoke is a complex mixture of more than 4000 chemical constituents (Villablanca 2000). One of the most important is nicotine (Stedman 1968). Exposure to nicotine was found to stimulate neutrophils to release elastolytic enzymes (Murphy 1998).

Genetics

In 1977 Clifton reported three male siblings with AAA and suggested that there may be a heritable trait causing AAA (Clifton 1977). The pattern of inheritance was concluded to be autosomal dominant with incomplete penetrance (Tilson 1984). A gene mutation in one of the structural proteins of the connective tissue was suspected (van Vlijmen-van Keulen 2002) and several candidate genes were investigated, so far without convincing evidence for any specific gene (Powell 2003).

The methods to determine familial incidence of AAA are not uniform. Most studies are based on self-reporting questionnaire or interviews. In these studies, approximately 13% of patients with an AAA will exhibit a family history (Norrsgård 1984, Johansen 1986, Powell 1987, Johnston 1988, Cole 1989, Darling 1989, Majunder 1991, Verloes 1995, Lawrence 1998). In studies on ultrasound screening of siblings of patients with AAA, approximately 20% of brothers and 5% of sisters were reported to have an AAA (Bengtsson 1989, Collin 1989, Webster 1991, Adamson 1992, van der Lugt 1992, Adams 1993, Baird 1995, Jaakkola 1995, Fitzgerald 1995, Larcos 1995). The corresponding proportion found in **study IV** was 32% and 17% respectively. However, the only relatives examined were those that happened to live in the investigated area and were 65 – 75 years old. Therefore, the proportion of familial AAA in Norsjö may be even greater, had all relatives been investigated. Furthermore, studies on familial incidence are usually based on large and clinically evident AAAs (Norrsgård 1984, Johansen 1986, Powell 1987, Johnston 1988, Bengtsson 1989, Collin 1989, Cole 1989, Darling 1989, Majunder 1991, Webster 1991, Adamson 1992, Adams 1993, Fitzgerald 1995, Jaakkola 1995, Larcos 1995, Baird 1995, Verloes 1995, Lawrence 1998). Patients with familial AAAs tend to be younger (Darling 1989) and may be over-represented among those with large AAAs. In **study IV** there was a trend towards larger AAA-diameters when a familial AAA was present. Two population-based cross-sectional studies on familial incidence of AAA were

published previously (Jamrozik 2000, Lederle 2000); the incidences were lower than in the present study. In conclusion, familial AAAs are more common in the Norsjö municipality compared to previous population-based studies, and the odds ratio for having an AAA when having a first degree relative with an AAA, was higher (Jamrozik 2000, Lederle 2000). The possible inherited predisposition observed in **study IV** seems to have a higher penetrance than in previous reports. This observation offers an explanation of the high prevalence found.

Inflammation

HsCRP has been suggested to be a marker for cardiovascular disease (Libby 2004). However, this association is confounded by mutual relationships of cardiovascular risk factors, including smoking habits and age (Rhode 1999).

The finding in **study IV**, that an elevated hsCRP level is an independent marker for AAA, is consistent with histological and biochemical findings in the literature (Powell 1987, Koch 1990, Vine 1991, Szekanecz 1994, Coggon 1996, Jones 2001, Tornvall 2003, Wiernicki, Vainas 2003). A chronic transmural inflammation is one of the principal histological features seen in AAA wall tissues (Koch 1990, Satta 1998). Matrix metallo-proteinases are thought to be the most important destructive enzymes within the aneurysm wall (Vine 1991). Interleukin-6 (IL-6), one of the inflammatory cytokines mediating matrix metalloproteinase expression (Szekanecz 1994) also acts as the most important stimulator of CRP production within the liver (Tornvall 2003). Powell and co-workers found aortic aneurysm to be an important source of circulating IL-6 (Jones 2001) and reported increased levels of CRP in patients with AAA compared with patients with occlusive aortic disease (Powell 1987). In a study by Wiernicki *et al*, an association between elevated CRP in AAA-patients and a specific Haptoglobin phenotype was found (Wiernicki 1999). In a recent study from the Netherlands a correlation between hsCRP and aneurysmal size was observed, and CRP mRNA was found in 25% of AAA tissues (Vainas 2003).

The observation in **study IV**, of a significant elevation of hsCRP-levels over time (mean time 11.6 years), in AAA patients, is novel. The elevation of hsCRP was equally pronounced in small AAAs as in large AAAs and indicates a dynamic inflammatory process involved in the early phase in the pathophysiology of AAA.

Interactions

Atherosclerosis, smoking and having a 1st degree relative with AAA were all associated with AAA in **study IV**. The more of these factors were present, the higher the prevalence. The OR was 32 when all three factors were present. This observation indicates that the three factors are independently asso-

ciated with AAA, and additional or even multiplicative effects of these factors were present.

This observation underlines the complexity of the disease and the possibility of a gene-environment interaction as an important cause of AAA. In the search for a genetic basis for the disease this should be taken into consideration.

Screening for AAA

Cost-effectiveness of screening for AAA

The efficiency of screening for AAA has been studied in three randomized clinical trials. The Chichester study (Vardulaki 2002) was the first to start in 1988, and randomized more than 6 000 men and women until 1999. They used 6 cm as threshold diameter for elective surgery. The relative reduction in AAA-mortality peaked at 4 years (52%) and declined to 21% at 10 years. Eighteen of 24 AAA-deaths were non-attenders or non-compliers.

The Viborg study from Denmark (Lindholt 2002) started in 1994, and has included 12 600 men. They used 5 cm as threshold diameter for elective surgery, and found the largest reduction in AAA-mortality at a very low cost. These calculations are, however, based on several questionable assumptions.

The MASS-trial, from the UK (MASS 2002) is the largest and most recent study. They have randomized more than 67 000 men. They used 5.5 cm as threshold diameter for elective surgery, based on the findings in the UK Small Aneurysm Trial and the ADAM-study (UK Small Aneurysm Trial 1998, Lederle 2000). After 4 years, a 42% risk reduction in AAA-mortality was observed and the NNT (or the number needed to screen to prolong one life) was 710.

Another prospective population-based evaluation of screening is the Huntingdon study (Wilmink 2003), based on a stepped wedge design. Over a nine years period, from 1991, the male population > 50 years was gradually screened, and until screening they acted as control group. For the first five years, 610 men had to be screened and three elective repairs had to be done to save one life. Thus, the NNT was 610.

In **study V**, 100 65-year old men needed to be screened and one elective repair undertaken to save two life-years. That would correspond to an NNT of approximately 800.

Table 18. Main outcome in clinical screening studies and study V.

Study	Age (year)	Follow-up (year)	AAA-death (%)	r-AAA (%)	Non-rupt op (%)
Chichester	65 - 80	4	- 52	- 55	+ 450
MASS	65 - 74	4	- 42	- 49	+ 250
Viborg	63 - 75	5	- 72	- 70	+ 278
Huntingdon	> 50	5		- 64	+ 100
Study V	65	35 *	- 35	- 45	+ 145

* In the Markov model the subjects were followed until death or 100 years of age.

Thus, several clinical studies have demonstrated that screening elderly men for AAA substantially decreases the rupture rate, with a significant reduction in AAA-mortality (Lindholt 2002, Vardulaki 2002, MASS 2002, Wilmink 2003). Today, with our health care system facing financial problems, the main concerns regarding a screening program for AAA is the long-term cost.

Evaluation of the cost-effectiveness would require a large randomized multicentre trial, running for several years. Furthermore, several of the variables in such a trial would be of local nature. For example; prevalence of the disease, the degree of opportunistic detection, nature of the screening program (single scan or repeated examinations), attendance rate, mortality associated with elective and emergency surgery, age of the invited population, indications for surgery and costs. These are all important factors that have influence on outcome.

Using the methods of decision analysis allow us to simulate screening programs and study cost-effectiveness for different scenarios. Derived from operations research and game theory during the 1950s, the method has complex mathematical origins and demand computer aid. In 1983, Beck and Pauker described the use of Markov models in medical applications (Beck 1983). Compared to a simple decision tree a Markov model allows long time periods to be modeled, in which risk of events are continuous, and the timing of an event is uncertain.

The Markov model structure in **study V** contained few health states and the outcome showed good agreement with findings in controlled empirical studies. The results were robust as shown in various sensitivity analyses. However, variations of a few key parameters affected the cost-effectiveness substantially, particularly the risk of rupture and long-term survival. The analyses showed that the cost-effectiveness was rather insensitive to variations in the cost of screening and surgery. The acceptability curves were steep, indicating small variance in cost-effectiveness ratio. The result should, however, be interpreted with caution since no information about the distributions of the mortality or costs assumptions were included.

The analyses also showed that the attendance rate had very little impact on the cost-effectiveness ratio. This may however not be the case if the non-

attenders are different from the attenders. Some previous studies indicate that persons not coming to screening for AAA have a similar overall mortality and risk of AAA as a control-population (Scott 1995, Ashton 2002), while others indicate that non-attenders are less healthy than attenders (Janzon 1986, Ögren 1996). Higher attendance rate means that the average screening cost per person will be lower. On the other hand, the analyses have indicated that the life expectancy of the screened persons is a key variable for the cost-effectiveness ratio. Thus a paradoxical effect could occur: If persons who attend the screening are healthier than those who do not attend, the cost-effectiveness could increase with a decrease of the attendance rate. This would, however, have a negative impact on another important goal in health-care, that of equality.

The natural course of AAA is difficult to study. Information obtained from studies on patients with small AAAs or on patients unfit for surgery provide incomplete information, due to differences in the studied populations. In most models of screening for AAA the estimated rupture- and surgery rates are based on the reported average expansion pattern. In **study V**, the estimated incidences of rupture of AAA and of surgery for non-ruptured AAA were based on clinical studies. The findings in these studies were extrapolated to assess the long-term consequences and the estimates were validated against clinical observations.

Previously published reports on cost-effectiveness of screening for AAA are heterogeneous concerning several important criteria making it difficult to compare the results, *table 19*. Most previous studies have found screening elderly men (65 years and older) to be cost-effective (StLeger 1996, Wilmink 1999, MASS 2002, Lee 2002, Lindholt 2002, Boll 2003).

The difference in cost-effectiveness seen between studies could be explained by differences in study- or model design and in differences in assumed probabilities. Factors found important in **study V**, e.g. opportunistic detection of AAA and additional mortality in AAA patients were excluded in some studies (StLeger 1996). Other differences are the age of the screened population, the discounting of costs and benefits, criteria for elective surgery, and inclusion of ruptured AAA occurring outside hospital (Frame 1993, Wilmink 1999, Lindholt 2002). Some studies are oversimplified and lack important information in the report, making the understanding and interpretation of the results difficult (Mason 1993, Boll 2003).

Table 19. Cost-effectiveness studies on screening for AAA

Author	Design	Setting	Estimated cost / LYG \$ in 2003 value**
Boll	Markov model	Netherl.	1 500
Frame	Model	USA/Canada	36 500
Lee	Markov model	USA	11 500
Lindholt	Randomised trial	Denmark	1 500 after 5 years follow-up
Mason	Model	UK	No screening dominates
MASS	Randomised trial	UK	52 500 after 4 years follow-up
MASS***	Randomised trial	UK	15 000 after 10 years follow-up
Pentikainen*	Monte Carlo model	Finland	10 500
St Leger	Model	UK	3 000
Swedenborg	Model	Sweden	3 500 / saved life
Wilmink	Population screening	UK	2 000 after 3 years follow-up
Study V	Markov model	Sweden	10 500

* Screening 1st degree relatives

** Costs updated to \$ 2003 value using currency exchange rates and the Swedish consumer price index

*** Projection at 10 years

QoL effects related to screening

Both the knowledge of having an AAA and surgery for AAA may have significant effects on QoL. Today (with no screening) 30% of persons with an undetected AAA at 65 years will eventually suffer from rupture or have surgical repair of the aneurysm, according to the assumptions made in **study V**, a proportion also seen in a follow-up study in Finland (Biancari 2002). Thus, 70% will be free from rupture or surgery and be “happily” unaware of the disease. With screening, the corresponding proportion would be 62%, with a condition not requiring treatment but where the knowledge may constitute a permanent source of anxiety. Therefore, not only changes in survival, but also changes in QoL have to be assessed. In recent years, the concept of QALY, which combines changes in these two outcomes, has been adopted in cost-utility analyses.

QoL is widely used in clinical trials and has now become a standard endpoint (Koller 2003). Numerous questionnaires assessing somatic, psychological and social aspects of patients’ well-being and functional capabilities are available. There are two types of measures: Generic and disease-specific measures. Generic measures are designed for different health problems in any population sample, while disease-specific measures assess specific diagnostic groups (Patrick 1989). Some generic measures, such as the Rosser Scale (Rosser 1988), yield a single index value. Such an index can be used to calculate QALY, to be used in cost-utility analyses. There is, however, no data available on the utility, in terms of QALY, among persons with AAA.

The SF-36 (Ware 1992) has become the most widely used generic QoL measure and has been recommended for use in vascular disease-related QoL assessments and outcome analyses (Beattie 1997). Its validity and reliability is thoroughly investigated and population normative data are available (Sullivan 1994). However, SF-36 does have limitations, for instance: physical function measure activities such as walking or kneeling, excluding integrated activities such as cooking, driving and ironing (Beattie 1997). The most important concern with a generic instrument, such as SF-36, is that it may be unresponsive to changes specific to AAA-screening.

The findings in **study III** are consistent with one of the two previously published studies with similar study design. Among 127 patients with small AAAs, Lindholt *et al* found that the diagnosis seemed to impair QoL permanently and progressively in conservatively treated cases (Lindholt 2000). They used a modified generic instrument called ScreenQL, based upon reported psychological consequences of screening and other existing questionnaires. Although it may be advantageous to use an instrument constructed for the specific purpose we believe the disadvantage predominates, not being able to compare the results with other studies or norms. As part of the Gloucestershire Aneurysm Screening Programme, Lucarotti *et al* performed the other prospective study (Lucarotti 1997). In their study of 61 AAA-patients, communicating the diagnosis did not decrease QoL. They did however only measure QoL one month after screening.

Indirectly one can interpret the results from several investigations (Magee 1992, Perkins 1998, Hennessy 1998, Malina 2000), including the large UK Small Aneurysm Trial (UK Small Aneurysm Trial 1998), as if establishing the diagnosis has a negative influence on QoL. They all conclude that surgery improves QoL compared to surveillance but QoL was not measured before the diagnosis in any of these studies. Investigating more than 500 AAA-patients, the Multicentre Aneurysm Screening Study (MASS 2002) indicates that the observed improvement in QoL after surgery represents a return to normal QoL as it was before screening and similar to those healthy at screening. Studies of AAA and QoL are summarized in *table 20*, also illustrating the problem of different generic scales.

As stated above, SF-36 may be unresponsive to changes specific to AAA-screening and a combination of generic and disease-specific tools has been advocated (Nanda 1998). Therefore, AAA-screening specific questions were designed as a complement to SF-36 in **study III**. This questionnaire is not validated and together with the lack of specific tools it precludes comparisons with previous investigators, limiting the possibility to draw conclusions. However, some remarks can be made: Twice as many relatives as patients were anxious about the AAA. Retrospectively only one of 24 patients would have preferred not to be informed about the AAA. All patients were satisfied with the information given to them but this may partly be a result of the study setting, and may be difficult to achieve in a large-scale screening program.

Table 20. Studies on quality of life among patients with AAA

Author	Objective	N	Measuring tool	Major conclusions
Hennessy	Elective v/s emergency surgery	14	Rosser index	Good QoL after surgery. No difference between the groups.
Joseph	Emergency surgery	26	SF-36	Same or better QoL compared to norms
Khaira	Screening	45	HADS	No differences in QoL between non-AAA, small AAA or large AAA
Lindholt	AAA-screening and conservative treatment *	127	ScreenQL	Communicating the diagnosis caused impaired QoL, reversible by surgery
Lucarotti	AAA-screening *	61	GHQ	Invitation to be screened causes mild anxiety, but not the diagnosis
Magee	Elective v/s emergency surgery	131	Rosser index	Retained good QoL after elective surgery but impaired QoL after emergency surgery
Malina	Endovascular v/s open surgery	40	NHP	Better QoL after surgery than before. No difference between endovascular and open surgery
MASS	AAA-screening and surveillance v/s surgery	545	HADS, STAI, SF-36 and EQ-5D	In short term impaired QoL after diagnosis and surgery. In long term no effect of diagnosis and better QoL after surgery
Perkins	Elective surgery	59	SF-36 and Rosser index	QoL improved after surgery
Prinssen	Endovascular v/s open surgery	153	SF-36 and EQ-5D	In long term better QoL after open surgery
UK Small Aneurysm Trial	Conservative treatment v/s surgery	865	SF-20	Early surgery improved QoL compared to US surveillance
Study III	AAA-screening *	24	SF-36	Impaired QoL among those who have the disease with low QoL before screening, but not among those with normal QoL prior to screening

* compared QoL before and after screening. SF-36 = Short Form-36, HADS = Hospital Anxiety and Depression Scale, GHQ = General Health Questionnaire, NHP = Nottingham Health Profil, STAI = Spielberger state-trait anxiety inventory, EQ-5D = EuroQol-5D, SF-20 = Short Form-20.

The sub-analysis, of the effect of different baseline QoL, was not anticipated in the design of **study III** and one of the subgroups only consists of six patients. However, the results indicate that low QoL is a possible risk factor for negative effects on QoL of diagnosing an AAA by screening. Similar findings have been reported among women screened for breast cancer. The

most common reaction to diagnosis and early treatment is depression and anxiety, in one study seen in a quarter of the patients (Maguire 1987). Several authors reported that a history of depression and stressful events prior to diagnosis or surgery were predictors of psychiatric morbidity (Morris 1977, Hughes 1982, Dean 1987, Mausell 1992).

The results on individuals screened for breast cancer, as well as the findings of **study III**, on persons screened for AAA, suggest there is a group vulnerable to a positive diagnosis at screening. This finding poses important practical and ethical questions, since most patients with screening-detected AAA never will meet the criteria for surgical repair. Can those vulnerable to screening be protected? Is it reasonable to perform screening that is beneficial for most but harms some? Or should we follow the golden rule of "*primum est non nocere*"?

No clinical studies have assessed the cost-utility of screening for AAA. Although no data on the utility in persons with AAA was available, some preliminary analyses with QALYs as outcome measure were performed in **study V**, to get an idea of how this aspect would affect the cost-effectiveness. The cost per QALY gained was similar to the cost per life year gained if patients with AAA were assumed to have the same utility as the general population. However, if a reduced utility was assumed for patients having an AAA detected by screening, the cost-effectiveness was decreased seven-fold. This indicates that a possible QoL reduction due to worries in patients who are diagnosed with AAA is an important aspect to consider when evaluating the cost-effectiveness of AAA screening.

Different screening strategies

It is important to identify those patients who will benefit most from the screening, as help for selecting the most appropriate subjects as target for the examination. Male sex and old age are strong and independent risk factors for AAA (Bengtsson 1993, Lederle 2000) and thereby defines a proper risk group to be screened. **Study V** showed that the incremental cost per LYG for screening all 65-year-old men for AAA was lower than what is generally considered cost-effective (Johannesson 1998, Raftery 2001, Ekman 2002).

Although other screening strategies have been suggested, only screening of elderly men, with different age spectra, have been evaluated in clinical studies (Lindholt 2002, MASS 2002, Vardulaki 2002, Wilmink 2003), and in a Monte-Carlo model, Pentikainen *et al*, found screening of 1st degree relatives to be cost-effective (Pentikainen 2000).

The assessment of different screening strategies in **study V**, indicate that screening 60-year-olds with re-screening after 5 years results in a greater benefit in terms of life years gained, with a low additional cost per LYG, compared to screening 65- or 70-year old men once. About 66-83% of all ruptured AAA occurs in men and 81-87% of whom will be over 65 years of

age (Birkerstaff 1984, Wen 1996, Choksy 1999, Swedvasc 2003). Thus, 53-72% of all potential ruptured AAAs would be found among men above 65 years, who represents only 7% of the total population (SCB). By screening 60-year-olds, an additional 10% of all AAAs that may rupture could be detected (Birkerstaff 1984, Wen 1996, Choksy 1999, Swedvasc 2003). The data on AAA in 60-year-olds is uncertain, however, since most screening studies included older persons. This result stresses the importance to evaluate different screening strategies in future clinical studies and to define the optimal age group.

Study V demonstrated that the cost-effectiveness would be even better if appropriate risk groups were chosen for screening. Relatives to AAA patients, patients with claudication or angina pectoris as well as smokers are suitable for screening. It was estimated that 18% of siblings to AAA-patients have an AAA (Bengtsson 1989, Collin 1989, Webster 1991, Adamson 1992, van der Lugt 1992, Adams 1993, Baird 1995, Jaakkola 1995, Fitzgerald 1995, Larcos 1995), representing approximately 1.5% of all AAA and found in 0.5 % of the population. Thus, it is important not to confuse cost-effectiveness and the proportion of ruptured AAA that can be prevented by screening. If the main purpose is to prevent as many ruptured AAA as possible only age and male sex should be used in selecting risk groups for screening. If the purpose is to prevent rupture as cost-effectively as possible other riskgroup may be considered.

Data on screening **women** for AAA is scarce. **Study I** is one of few screening studies that have also studied the female population (ref). Although the prevalence is lower among women, and in the Swedvasc registry only 15% of the patients operated on for AAA are female (Swedvasc 2003), life expectancy and the risk of rupture are greater among women. On the other hand women with AAA often have multiple diseases. Future studies on female AAA, and on the possible impact on screening, are warranted.

Study V also showed that prevalence and life expectancy are two factors influencing the cost-effectiveness in different directions. The prevalence of AAA in smokers and in patients with claudication or angina, for example, is higher than in the general population (Smith 1993, Pleumeekers 1995, Alcorn 1996, Kanagasabay 1996, Jamrozik 2000), but the long-term mortality is also higher (Dormandy 1999, Kilander 2001). The trade-off between high AAA prevalence and lower life expectancy eliminates most of the expected additional benefits of screening such high-risk groups selectively. In younger persons the situation is opposite: the prevalence of AAA is lower and the life expectancy is longer.

The effect of prevalence on cost-effectiveness was almost exponential initially but leveled rapidly when the prevalence rose above 5%. This explains the rather surprisingly low additional benefits observed when patients with popliteal aneurysm were screened. *Figure 9* displays the impact of prevalence and relative long-term survival on cost-effectiveness.

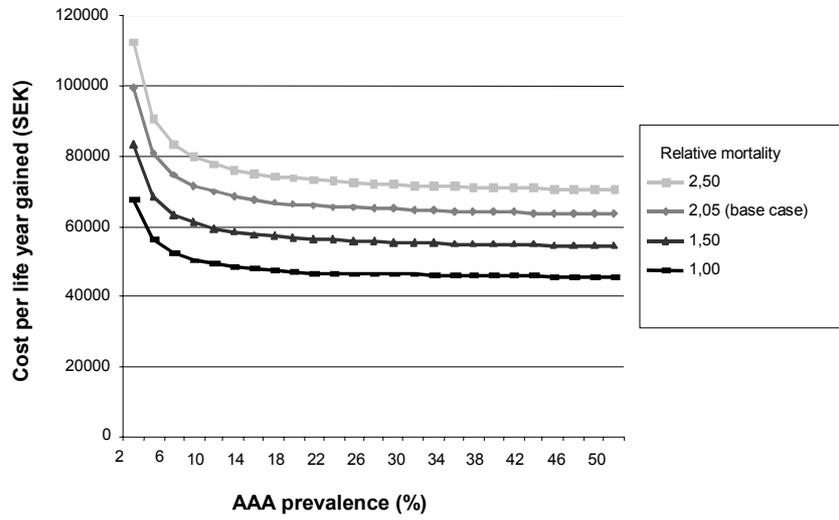


Figure 9. Impact of AAA prevalence and relative mortality on cost-effectiveness

CONCLUSIONS

The highest prevalence of AAA ever reported, in a population-based screening program, was found. On the basis of these findings the entire population of the Norsjö municipality is considered at high-risk of AAA.

The prevalence was highly dependent on the diagnostic criteria, the definition of AAA as well as on the age and sex of the investigated subjects.

A significant difference between diameters measured with US and CT was found. US overestimated the diameter among subjects with non-aneurysmal aortas, while no difference of the mean value was seen in aneurysmal aortas. The variability between measurements by US and CT was greater for aneurysmal aortas and for the transverse diameters.

Elevated levels of triglyceride, LDL- and total cholesterol at age 60 were associated with screening detected AAA after a median of 12 years of follow-up. At screening, the risk of having an AAA was associated with male sex, high age, current smoking, having a first-degree relative with AAA and atherosclerosis. A significant increase of hsCRP over time was observed in AAA patients, indicating that inflammation may be an important factor in the development of AAA.

The relationship with atherosclerosis was complex and interrelations with several known atherosclerotic risk factors were observed. Among traditional risk factors for atherosclerosis some were associated with AAA, others not, indicating complex and partly different etiological mechanisms. An additional risk was observed when more than one risk factor was present.

Screening 65-year-old men for AAA may be cost-effective, while screening younger men with a re-screening could be equally cost-effective with the advantage of more life year gained (LYG). The trade-off between high AAA prevalence and lower life expectancy in high-risk groups, such as smokers and persons with angina or claudication, eliminates most of the expected additional benefits of screening these groups selectively

Variations of risk of rupture among screened and non-screened as well as differences in long-term survival affected the estimated cost-effectiveness

substantially. The cost-effectiveness was rather insensitive to variations in cost of screening, cost of surgery and attendance rate.

Screening for AAA resulted in impairment of mental health among those who had the disease and who suffered a low QoL prior to screening. Among those who had an age-adjusted normal QoL prior to screening, and who were found to have the disease, as well as those who were found to have normal aortas, no negative effect on QoL was observed.

If a reduced utility, in terms of QALY, was assumed for patients having an AAA detected by screening, a substantial reduction in cost-effectiveness was observed. A possible QoL reduction due to worries in patients who are diagnosed with AAA may have an important impact on the cost-effectiveness of AAA screening, and merits further investigation

Further factors that need better characterization, in order to reduce the uncertainty about the costs and consequences of screening for AAA, are the natural course of AAA detected by re-screening and the age-specific natural course of the disease.

SUMMARY IN SWEDISH (Sammanfattning på svenska)

Abdominelt aortaaneurysm (AAA) är en sjuklig vidgning (bråck) av stora kroppspulsådern i buken. Det finns ingen enhetlig definition av ett AAA men anses vanligen föreligga om kroppspulsåderns diameter överskrider 30 mm. Sjukdomen är relativt vanlig, framför allt hos äldre män där ca 5 % beräknas ha sjukdomen. Med tiden vidgas bråcket alltmer för att så småningom brista (ruptur). Endast 1/3 av de individer som drabbas av ruptur når sjukhus och kan opereras. Av de som opereras överlever drygt hälften, ofta med lång intensivvård i efterförloppet. Den totala dödligheten vid ruptur är därför ca 80 %, vilket motsvarar nära 2 % av dödsfallen hos män över 60 år. I Sverige dör totalt uppskattningsvis 1000 individer årligen i AAA.

För att förebygga ruptur rekommenderas operation i lugnt skede. Operationen består i att man ersätter den sjuka delen av kroppspulsådern med en konstgjord så kallad kärldraft. Dödligheten vid ett planerat ingrepp är under 5 %. Då sjukdomen i regel är helt utan symtom upptäcks dock sjukdomen endast hos ett fåtal, och då som ett bifynd vid exempelvis ultraljudsundersökning vid misstanke om någon annan sjukdom. Mass-undersökning (screening) av äldre män kan därför vara ett sätt att minska dödligheten i ruptur av AAA.

Vid Skellefteå lasarett opererades ovanligt många patienter med AAA, och många av dessa kom från Norsjö, en liten kommun i Västerbottens inland. Sjukdomen misstänktes vara ett allvarligt hälsoproblem, särskilt mot bakgrund av att också relativt sett fler hade opererats för ruptur. Även befolkningen i Norsjö och sjukvårdspersonal vid den lokala vårdcentralen upplevde att AAA var ett allvarligt problem. En screening studie genomfördes för att kartlägga förekomsten av sjukdomen. Tänkbara risk-faktorer för AAA studerades liksom hur vetskapen om att man har ett AAA påverkar livskvaliteten. Samtliga män och kvinnor mellan 65 och 75 år erbjöds att delta i en ultraljudsundersökning (UL). Uppslutningen var 91%, och av 502 deltagare undersöktes 92 personer också med datortomografi (CT) pga svårigheter vid UL eller om diametern av kroppspulsådern överskred 28 mm.

I **delarbete I** sågs ett AAA, definierat som en diameter om 30 mm eller mer, hos 17 % av männen och hos 3,5 % av kvinnorna. Förekomsten varierade 10-faldigt beroende på vilka diagnostiska kriterier som användes och 70 % av AAA sågs hos de som var 70 år och äldre.

I **delarbete II** jämfördes mätvärdena från UL och CT. Betydande variationer uppmättes mellan mätmetoderna. Beroende av mätplan och aortadiameter skiljer sig värdena mer än 5 mm hos 24-50 % av de undersökta individerna. Detta kan avgöra om en person anses sjuk eller inte och om operation anses nödvändigt eller inte. Medvetenhet och lokal utvärdering av teknikernas brister rekommenderas.

I **delarbete III** studerades livskvaliteten före undersökningen och ett år efter med hjälp av enkäter. Ingen negativ effekt av screening sågs bland patienter med AAA som hade normal livskvalitet före screening eller hos de som inte hade ett AAA. Däremot försämrades den mentala hälsan hos de som befanns ha ett AAA och som hade låg livskvalitet före screeningundersökningen.

I **delarbete IV** studerades tänkbara riskfaktorer för AAA. I blodprover tagna 11 år före screening sågs högre kolesterol värden hos de som befanns ha ett AAA vid screening. Vid screening var rökning, förekomst av åderförkalkning och förekomst av en förstagsgrads släkting med AAA förenat med ökad risk för AAA. Sambandet med åderförkalkning var komplicerat med delvis gemensamma riskfaktorer. Jämfört med blodprover tagna 11 år före screening och blodprover tagna i samband med screening sågs stigande inflammationsmarkörer hos AAA patienterna.

I **delarbete V** studerades kostnadseffektiviteten för olika screeningstrategier av män. Baserad på en systematisk litteraturgenomgång analyserades kostnaden per vunnet levnadsår i en datasimulerad s.k. Markov modell. Kostnaden varierade mellan 60 000 och 100 000 SEK beroende på ålder (60-, 65-, eller 70 år), riskgrupp (alla män eller högrisk grupper som rökare, patienter med kärlkramp, syskon till AAA patienter eller patienter med pulsåderbräck i benet) och om undersökningen upprepades eller inte. Kostnaden per vunnet levnadsår uppskattades till 75 000 SEK om 65-åriga män screenades en gång. En eventuellt nedsatt livskvalitet beroende på screening påverkade kostnadseffektiviteten avsevärt i negativ riktning.

Sammanfattning: I en massundersökning av Norsjös äldre befolkning har världens högsta förekomst av AAA hittats. Ett samband mellan rökning, åderförkalkning och AAA sågs och genetiska faktorer samt inflammation kan ha betydelse vid utveckling av AAA. Att screena 65-åriga män för AAA räddar liv till en rimlig kostnad, men effekten på livskvaliteten behöver studeras ytterligare.

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