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ABDOMINAL AORTIC ANEURYSM

– UNCHARTED ASPECTS OF RUPTURE

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Department of Molecular Medicine and Surgery

Abdominal Aortic Aneurysm

– uncharted aspects of rupture

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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I think I started something

– Frank Ocean

De sa en dag ska vi alla dö
Jag sa alla andra dar ska vi inte det
– Lorentz

Till mina tjejer

LMTH

ABSTRACT

Unlike intact abdominal aortic aneurysm (iAAA), ruptured abdominal aortic aneurysm (rAAA) is a lethal condition demanding immediate resuscitation and surgical intervention. Where the former is a silent disease with slow expansion of the infrarenal aorta, rAAA is symptomatic with abdominal/back pain and possibly even hemorrhagic shock. Repair of an iAAA has low mortality rates while repair of rAAA is associated with much higher complication rates and postoperative mortality.

In Sweden, the prevalence of iAAA amongst 65-year-old men is 1.2–1.5 %. Every year 175–200 patients with rAAA are treated at hospitals across the country. With decreasing autopsy rates, the overall number of ruptures remains unknown and many studies lack the reporting of untreated patients.

The overall aim of this thesis was to investigate less commonly studied aspects of AAA epidemiology, with particular emphasis on rAAA; from broad epidemiology with time trends in incidences and repair modality, to population-based investigations of the prevalence of previously known AAA in patients with rupture. Furthermore, the effect of sex and socioeconomic position (SEP) on the severity of disease and outcome of repair was studied.

Studies I and II are retrospective population-based studies of all individuals with a rAAA admitted to a hospital in the Stockholm county region and Gotland county, 2009–2013. The aim of these studies, based on a study cohort of all admitted rAAA patients, was to explore the proportion of untreated rAAA patients, and of previously diagnosed AAA patients that are found in a cohort of ruptured patients. Study I demonstrated that the majority (75 %) of patients with rAAA who reach an emergency department will undergo corrective repair. Repair rates, modality of repair and outcome were similar between the sexes. Study II showed that one third of patients with rAAA had a previously known aneurysm and the most common reasons for not having undergone repair included denied elective surgery (36 %), missed surveillance (31 %) and patient choice (18 %).

Study III is a population-based study of 41,222 patients nationwide that aimed to investigate if low SEP was associated with presenting with a rAAA rather than iAAA and with poorer repair outcome. Also, the study describes time-trends in AAA incidence and rAAA mortality for 2001–2015. After adjustment for age, sex and comorbidity a continued strong association between low SEP and the risk of presenting with a rAAA and dying within 90 days of repair persisted.

Study IV, also a nationwide study, included 10,724 patients with rupture. Using a propensity-score-matched analysis, women were matched with men and an analysis was performed to determine whether: women are less often treated for their rAAA; women are less often treated with EVAR; outcome after repair is worse for women compared to men. The average treatment effect for women was -0.08, p<.001 for receiving repair and 0.086, p<.001 for 90-day mortality. However, when adjusting for postoperative complications, only short-term mortality was higher in women. No difference in repair modality was seen between the sexes. Complication rates were similar between the sexes. Time trends indicate a decrease in the number of rAAA among men, especially aged 65–84, in contrast to the unchanged rates in women.

The incidence of AAA overall and rAAA specifically is declining while the use of EVAR in ruptures is increasing. On a regional level, sex differences in rAAA were not evident but nationwide sex differences were prominent and alarming. Apparent positive trends in the care of men with rAAA can be found that are partly associated with the implementation of screening and with improved cardiovascular prevention in the population. However, the results unfortunately do not reflect equally in the female population. Alarmingly, our results emphasize the presence of inequality in the health care system for women and those with low income and a low level of education.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Stora kroppspulsådern (latin: aorta) är kroppens största blodkärl och transporterar blod direkt från hjärtat ut till kroppens alla organ inklusive hjärnan, njurarna, tarmarna samt extremiteterna (armar och ben). Abdominala (buk) kroppspulsådern, som denna avhandling berör, löper från diafragman ner till delningen till de två stora bäckenkärlen .

Abdominala aortan kan, av olika anledningar, långsamt börja vidgas, som en ballong. Denna process sker oftast helt i det dolda utan att ge individen några som helst symptom. De tre största riskfaktorerna för denna utveckling är rökning, hög ålder och manligt kön. När abdominala aortan vuxit till 3 cm i diameter kallas det abdominalt aortaaneurysm (AAA), som helt enkelt betyder utvidgning av aortan. När man utvecklat ett AAA så fortsätter det oftast att öka i storlek, med cirka 2,5 mm/år. Baserat på kunskap från flera större internationella studier är rekommendationen att man ska överväga kirurgisk behandling av patienter med AAA när aneurysmet vuxit till 5–5,5 cm i diameter. Man bedömer då att risken för att den ska spricka (rupturerat AAA, rAAA) och orsaka en livshotande blödning är större än riskerna med behandling. Har patienten hög risk för kirurgiska komplikationer, till exempel svår hjärtsjukdom, kan behandlingsgränsen höjas. De patienter som behandlas med ett planerat kirurgiskt ingrepp för sitt AAA har låg komplikationsfrekvens och bra överlevnad. De patienter som inkommer med ett rAAA har mycket sämre överlevnad.

I dag finns två olika metoder att välja mellan vid operation av ett AAA/rAAA. En öppen operation innebär att patienten sövs och man öppnar buken från bröstbenets nedre utskott hela vägen till blygdbenet och kroppspulsådern ersätts med ett tubformad syntetiskt material. En endovaskulär metod (EVAR) finns också att tillgå. Denna innebär att man via små nålstick i ljumskarna leder fram smala vajrar med klädda med en protes som man löser ut på insidan av aortan och på så sätt täcker för aneurysmet/rupturen och leder blodet rätt. En av fördelarna med EVAR är att ingreppet går att utföra i lokalbedövning.

I vår första studie undersöktes hur stor andel av personer som inkommer med rAAA som erbjuds kirurgisk intervention, och hur den gruppen skiljer sig från de obehandlade med avseende på till exempel ålder och könsfördelning. Vi fann att en mycket större andel av patienter som inkommer med rAAA behandlas med kirurgisk intervention än det som tidigare beskrivits i litteraturen. De som nekas behandling var äldre, men kvinnor behandlades i lika hög utsträckning som män.

Den andra studien ämnade till att undersöka andelen tidigare kända AAA hos patienter som söker med rAAA på en akutmottagning i Stockholms läns landsting. Anledningar till att man inte behandlade patienten innan rupturen hann ske undersöktes. En tredjedel av patienterna med rAAA hade ett tidigare känt AAA som av olika anledning hade missats i uppföljningen i vården vilket tyder på brister i samordningen kring AAA-patienter i länet.

Den tredje studien är en nationell studie som undersökte sambandet mellan låg socioekonomisk position (SEP) och risk att man inkommer med ruptur i stället för ett icke-rupturerat AAA första gången man får sin AAA diagnos. Vidare undersöktes sambanden mellan låg SEP och överlevnad efter behandling för rAAA. Här sågs att låg SEP var associerat med högre risk att söka med rAAA vid första diagnosen och sämre överlevnad efter åtgärd.

Den fjärde och avslutande studien återkom till könsskillnader vid rAAA. Här användes ett landsomfattande material på över 10 000 patienter med rAAA och fynden kan delas upp i tre delar; 1. Kvinnor erhåller i lägre grad behandling vid rAAA än män. 2. Inga skillnader i typ av behandlingsmetod vid rAAA sågs mellan könen och 3. Kvinnor har sämre överlevnad, inom främst 30-dagar från operation.

Tillsammans belyser dessa fyra studier områden inom kärlkirurgin och AAA-sjukdom som tidigare inte förstärkts eller belysts med särskilt fokus på utsatta grupper i samhället. Förhoppningsvis leder resultaten oss ett steg framåt i förbättringen av vården för patienter med AAA.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals as indicated below.

I. **A majority of admitted patients with ruptured abdominal aortic aneurysm undergo and survive corrective treatment. A population based retrospective cohort study**
Rebecka Hultgren, Sayid Zommorodi, Moa Gambe, Joy Roy
World Journal of Surgery 2016; 40(12): 3080-3087

II. **High proportion of known abdominal aortic aneurysm in patients with rupture indicates surveillance deficiency**
Sayid Zommorodi, Joy Roy, Johnny Steuer, Rebecka Hultgren
Journal of Vascular Surgery, 2016; 64(4): 949-955

III. **Understanding abdominal aortic aneurysm epidemiology – socioeconomic position affects outcome**
Sayid Zommorodi, Karin Leander, Joy Roy, Johnny Steuer, Rebecka Hultgren
Journal of Epidemiology & Community Health, 2018; 72: 904-910

IV. **Propensity-score-matched analysis of sex differences in repair rates and outcome after ruptured abdominal aortic aneurysm**
Sayid Zommorodi, Matteo Bottai, Rebecka Hultgren
Manuscript submitted

TABLE OF CONTENTS

1 List of abbreviations 17
2 Introduction 19
2.1 Historical background 19
2.2 Definitions, anatomy and pathophysiology 20
2.2.1 Definition and anatomical landmarks 20
2.2.2 Pathophysiology 21
2.2.3 Morphology 21
2.3 Epidemiology 22
2.3.1 Intact AAA – prevalence and risk factors 22
2.3.2 Ruptured AAA – prevalence and risk factors 23
2.4 Clinical presentation 24
2.4.1 Screening 26
2.4.2 Improving care of AAA patients 26
2.4.3 Non-operative management of rAAA 27
2.5 Treatment 27
2.5.1 iAAA. Medical treatment and preoperative optimization 27
2.5.2 rAAA. Initial management 28
2.5.3 Surgical intervention 28
2.6 Outcome 30
2.6.1 Outcome of surgical intervention in iAAA 30
2.6.2 Outcome of surgical intervention in rAAA 31
2.7 Socioeconomic position 33
2.7.1 What it is and how to measure it 33
2.7.2 Income 33
2.7.3 Relationship status – it's complicated 34
2.7.4 Level of education 35
2.7.5 Index and context 35
2.7.6 SEP and surgical outcome 35
2.8 Let's talk about sex 37
2.9 Mapping the uncharted territories 37
3 Aims of the thesis 39
4 Data sources and methods 41
4.1 Overview 41
4.2 Data sources 42
4.2.1 The Swedish National Patient Register 42
4.2.2 The Swedish Cause of Death Register 42
4.2.3 The Swedish Vascular Register 43
4.2.4 Longitudinal integration database for health insurance and labour market studies (LISA) 43

4.3 Methods 44
4.4 Ethical considerations 45
5 Results and discussion 47
5.1 Results 47
5.2 Discussion 53
5.2.1 Untreated rAAA 53
5.2.2 Previously detected 54
5.2.3 When to treat AAA 54
5.2.4 Get rich or die trying 55
5.2.5 Sex differences 56
5.2.6 Outcome 56
5.3 Methodological considerations 57
5.3.1 External validity 58
5.3.2 Internal validity 58
5.3.3 Random error 58
5.3.4 Bias 59
5.3.5 Confounder 59
6 Conclusions 61
7 Future perspectives 63
8 Acknowledgements 65
9 References 67

1 LIST OF ABBREVIATIONS

Abdominal aortic aneurysm	AAA
Abdominal compartment syndrome	ACS
Aortic size index	ASI
Average treatment effect	ATE
Cause of death registry	CDR
Cerebrovascular lesion	CVL
Chronic obstructive pulmonary disease	COPD
Computer tomography	CT
Confidence interval	CI
Coronary artery disease	CAD
Vancouver Area Neighborhood Deprivation Index	VANDIX
Endovascular aortic repair	EVAR
Gross Domestic Product	GDP
Intact abdominal aortic aneurysm	iAAA
Intensive care unit	ICU
International classification of disease	ICD
Longitudinal integration database for health insurance and labour market studies	LISA
Matrix metalloproteinases	MMP
Millimeter	MM
Multiple organ failure	MOF
Myocardial infarction	MI
National board of health and welfare	NBHW
National Patient Register	NPR

Open repair	OR
Patient Reported Outcome	PROM
Propensity-score	PS
Propensity-score-matched	PSM
Renal failure	RF
Quality of Life	QoL
Randomized controlled trial	RCT
Ruptured abdominal aortic aneurysm	rAAA
Socioeconomic position	SEP
Swedish vascular registry	SWEDVASC

2 INTRODUCTION

2.1 HISTORICAL BACKGROUND

Deciphering the historical evolution of abdominal aortic aneurysm (AAA) disease and trailing the different methods of treating these "jumping vessels", as they were first described in the Ebers Papyrus dating back to 1550 BC, one soon realizes that what is modern and considered a break-through in medical science, is quickly forgotten and discarded when the next break-through comes along. From ancient rants to complete ligation of the aorta, followed by inducing fibrosis using cellophane. The latter method was used when surgeons treated Albert Einstein's AAA in 1948. He later died from a rupture seven years later.[1] Following that, surgeons and scientists from all over the world contributed to the evolution and refinement of treating AAAs. French surgeon Dubost performed the first successful resection of an AAA with restoration of blood flow using a homograft in 1951[2] and later that decade the use of vein grafts and vinyl tubes for the repair of AAA were reported.[3, 4] Coming to the agreement to actually treat AAA was monumental but reaching a consensus on when to treat is still in some aspects a matter of dispute. However remarkable the evolution in medical engineering for repair options for AAA was in the past, it is only in the last two decades that its repair and outcome has gone through a huge reform. After Volodos in 1986 and Parodi in 1991 described an endovascular approach to treating AAA, one might say the Rubicon was crossed.[5, 6] Outcome after repair of AAA has improved since then and more ruptures are now prevented on a national level with early detection strategies such as nationwide screening programs and meticulous surveillance regimes, as well as with cardiovascular risk optimization.

With that said, many questions regarding ruptured abdominal aortic aneurysm (rAAA) remain unanswered and unexplored. Hopefully and humbly, this thesis aims to answer some of these questions and shed light on previously uncharted epidemiological aspects of the rAAA.

2.2 DEFINITIONS, ANATOMY AND PATHOPHYSIOLOGY

2.2.1 Definition and anatomical landmarks

For the abdominal aorta a size more than or equal to 30 millimeters (mm) in men is often recognized as the definition of an AAA.[7, 8] This definition is based on ultrasound diameters with a sensitivity of 67 % and a specificity of 97 % in predicting the need for AAA repair within ten years.[9] Some studies have suggested 27 mm to be an adequate definition in women.[7, 10] Another accepted way of defining an arterial aneurysm is to assess its size compared to the size of an unaffected adjacent segment of the same vessel. A local widening of >1.5 times its expected normal size including all layers of the artery (intima, media and adventitia) defines it as an aneurysm.[11-13] The different ways of defining an AAA cause difficulties in comparing studies of the disease. The abdominal aorta is delimited cranially by the diaphragm, and is commonly further divided into the suprarenal (above the renal arteries) and infrarenal segments. Thus, there are suprarenal and infrarenal AAAs. Juxtarenal AAAs extend to the level of the renal arteries. The aortic bifurcation is the lower boundary. For the purpose of this thesis, the term AAA refers to the infrarenal AAA, *figure I.*

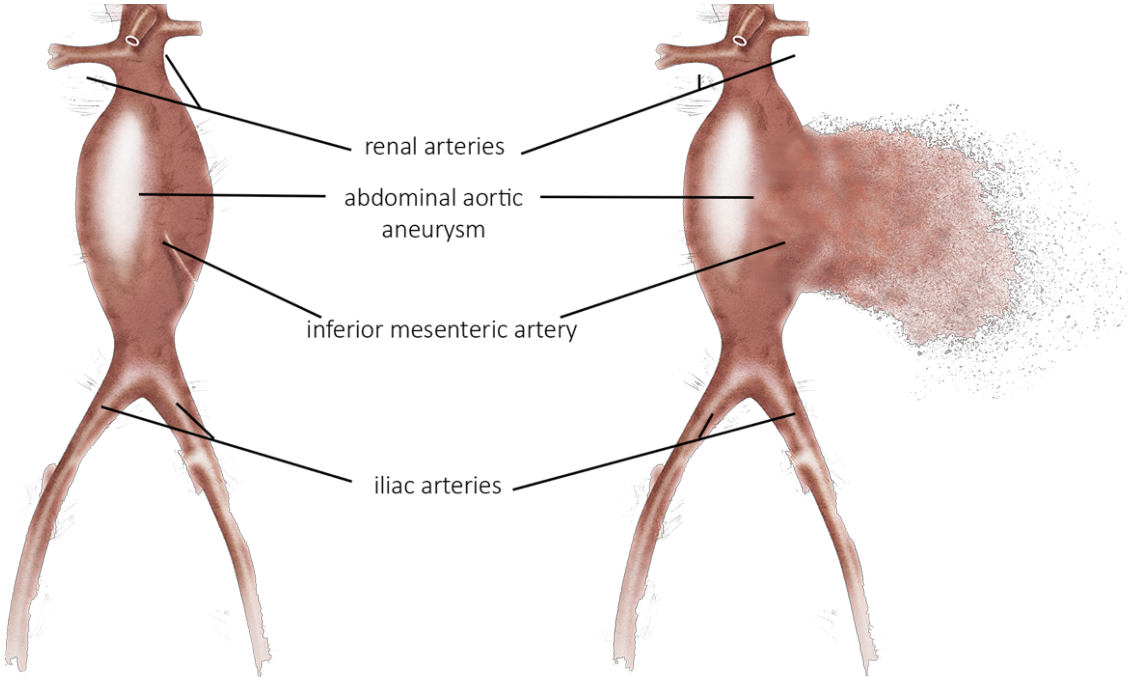

Figure I. Anatomical image of the intact abdominal aortic aneurysm (AAA) to the left and the ruptured AAA to the right.

2.2.2 Pathophysiology

The widening of the abdominal aorta is caused by a complex and not fully understood pathway leading to the weakening of the aortic wall with all three of its layers affected in the process. Proteolytic enzymes involved in inflammatory processes cause degradation of collagen and elastin in the aortic media as well as apoptosis of smooth muscle cells in the aortic wall.[14] Matrix metalloproteinases (MMPs), cytokines and reactive oxygen species are possible participants in this inflammatory degeneration of the aortic wall. The widened aortic wall contributes to turbulent blood flow and promotes the formation of intraluminal thrombus. This phenomenon is common in the pathophysiology and anatomy of an AAA and seems to play an important role in further weakening and degradation of the aortic wall.[15-17] Still, the true and full pathophysiology of AAA development remains unknown.

2.2.3 Morphology

The anatomical shape of an aneurysm further divides it into subgroups of fusiform and saccular aneurysm. The fusiform aneurysm is the most common shape in AAA and is seen as a symmetrical bulge involving the full circumference of the aortic wall*, figure II*. The common perception of saccular aneurysms as high risk aneurysm with higher rupture tendencies has rarely actually been studied. In an American setting, a study found similar growth rates in saccular aneurysms as in fusiform.[18] However, the current recommendation is that saccular aneurysm ought to be treated at smaller diameter than fusiform.[19, 20] Dilation of all three layers of the arterial wall defines the aneurysm as a "true" aneurysm. This is to separate it from false aneurysm, also known as pseudo-aneurysm. These are often formed after a penetrating trauma or blunt injury and occur as blood escapes the lumen of an artery to create a localized, encapsulated hematoma either between the media and adventitia or in the surrounding tissues.

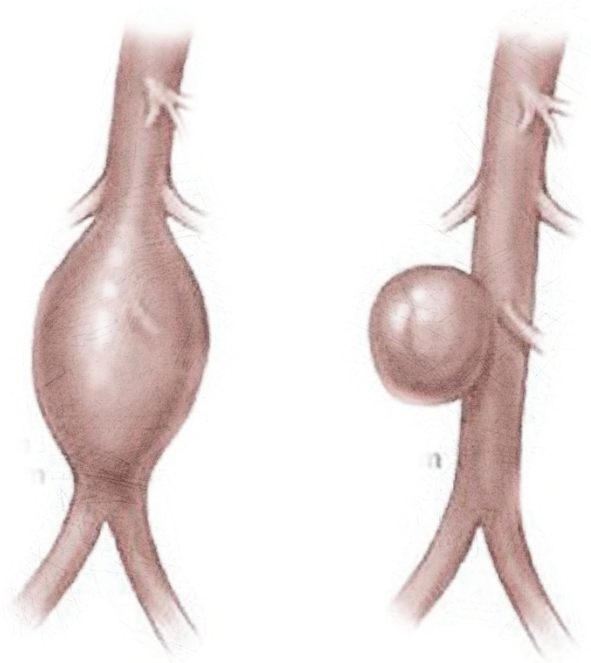

Figure II. A fusiform abdominal aortic aneurysm (left) and saccular AAA (right)

2.3 EPIDEMIOLOGY

2.3.1 Intact AAA – prevalence and risk factors

AAA is fairly rare in the general population and its prevalence seems to be decreasing[21] but it is still a burden on healthcare globally.[22] During the 20th century it was a disease on the rise with high mortality causing the vascular community to take action, conducting large randomized trials and cohort studies to reduce the knowledge gap of the disease.[23, 24] Now in the 21st century we are starting to see a reversed trend in epidemiology and mortality.[25-27] Large randomized screening studies have reported a prevalence of around 4–7.6 % amongst men aged 64 or higher.[28, 29] However, these data are outdated and more recent national studies in Sweden report on a much lower prevalence, not more than 1.5 % in 65-year-old men.[26, 30, 31] Approximately 2,000–2,500 new cases of AAA are seen each year in Sweden compared to 10,000 new cases of prostate cancers or 25,000 new heart infarctions annually.[32] The main risk factors associated with the development of AAA include smoking, advanced age, male sex and heritability.[33-37] Long-time smokers have been shown to have an up to eight-fold

increased risk of developing an AAA compared to never-smokers and the risk decreases with the number of years after smoking cessation[38-40] but increases with female sex.[41] The risk of developing AAA increases with age in both men and women.[33, 42] AAA has a much higher prevalence in men than women, with a ratio of 4–6:1.[34, 43-46] A meta-analysis has shown a higher risk of developing AAA in first-degree relatives of patients with known AAA[47] with twin registry studies reporting on a heritability as high as 70 %.[48, 49] More unclear and debated is the role of hypertension[50, 51], serum-lipid configuration[50-52] and atherosclerosis[24, 53] in the development of an AAA. An inverse association between diabetes and aneurysm growth has been shown.[39] The high prevalence of AAA in patients with coronary artery disease (CAD) indicates similar risk profiles and possible targets for sub-group screening.[54]

2.3.2 Ruptured AAA – prevalence and risk factors

Describing true epidemiological data on rAAA provides some difficulties. A proportion of patients, reported at around 50 %[55, 56], will die immediately at home. Estimations of out-of-hospital deaths are often based on death certificates[57] or autopsy reports that are declining[56-61]. With that in mind, incidence of rAAA is reported at 5.6–17.5 per 100,000 person-years[56, 58, 62, 63] with an overall mortality of rAAA around 80–94 %.[56, 64, 65] There has been, however, a decrease in mortality from rAAA reported since 1995.[27, 66, 67] This is sometimes accredited to a decreasing prevalence of AAA in the population which can be associated with changing smoking habits.[26, 68, 69] Also, the implementation of screening programs for AAA has been suggested as another cause of this decrease.[31] It is only in recent years that studies on rAAA have included data on both treated and untreated patients[70, 71], but there is an obvious need for further study in this field to answer questions such as how many of the AAA that rupture were previously known and what the reasons for non-repair at initial time of diagnosis were. The RESCAN study, a meta-analysis of >15,000 individuals with AAA, proposed different risk factors for growth and rupture, suggesting female sex, smoking and high blood pressure as risk factors for rupture and smoking as a risk factor for aneurysm growth.[39] Risk factors for aneurysm expansion also include high blood pressure, while diabetes and peripheral vascular disease seem to have a protective effect.[38, 44, 45] Also, hereditary AAA is associated with more rapid growth and higher rupture rate[72, 73] as well as rupture at smaller aneurysm diameter and at lower age.[73] The one variable used in clinical practice to predict the risk of rupture is the aneurysm size, or more precisely the maximum aneurysm diameter.[44, 45, 74] In a prospective study of 198 men with AAA of at least 55 mm in diameters, annual rupture risks were estimated

at 10 % for aneurysms 55–69 mm in diameter but >33 % for aneurysms >70 mm.[74] This is in contrast to a more recent pooled analysis of untreated AAA that suggests much lower rupture risks.[75]

Women have a higher risk of rupture than men.[39, 44, 46, 76] The reasons for this is debated, with possible weaker wall strength and a relatively higher aneurysm growth rate as two possible mechanisms.[10, 77] The expansion rate of an AAA seems to play a role in determining the risk of rupture[78, 79] but the influence of expansion rate on the choice to treat remains debated and it is not mentioned as a suggestion to treat on the basis of expansion rate in the latest guidelines from the American Society of vascular surgery.[19] Emerging data on the possible underestimation of the risk of rupture in women compared to men, implicates that the use of similar aneurysm diameter thresholds for both sexes for repair and surveillance could explain the increased risk in women.[80, 81] In recent years, new methods of estimating the rupture risk of an AAA have emerged including Aortic Size index (ASI)[80, 81] and biomechanical assessments of wall stress.[77, 82] However, the lack of prospective studies investigating these assessments has hindered these tools from being used in clinical praxis. Women have also been suggested to have a worse outcome after repair for rAAA than men.[83] This has however been refuted by other studies[71, 84-86] and the true association between female sex and outcome after repair remains unclear.

2.4 CLINICAL PRESENTATION

An iAAA is a silent disease; the patient rarely has any symptoms such as discomfort or pain. Sometimes a pulsating mass can be palpated over the umbilicus[87] but the AAA is most commonly found en-passant in routine scans for other diagnoses or in screening programs. When a patient is diagnosed they are referred to a vascular clinic for an assessment of the aneurysm and a general clinical evaluation at the prospect of a potential repair. Most AAAs found are small in size and the patients are put under an ultrasound surveillance schedule based on large studies assessing the rupture risk in relation to the maximum diameter of the AAA[23, 88-91], table I. These surveillance programs may differ between and within nations with regards to their surveillance intervals.

Table I. Detected aneurysm size and surveillance interval[19, 20]

Aneurysm size (mm)	Surveillance intervals
25-30	Rescan after 10 years
30-39	36 months
40-49	12 months
50-54	6 months

If or when the AAA grows to a maximum diameter of 55 mm, studies have shown that the annual risk of rupture exceeds the risks of surgical or endovascular repair.[88, 92] For women, the threshold for repair is lower, around 50 mm.[19] Preoperative planning of a patient with an AAA includes a computer tomography (CT) of the aorta, *figure III*, possible referral for optimizing cardio-, pulmonary- and renal status and an in-depth discussion with the patient regarding the different repair modalities available.

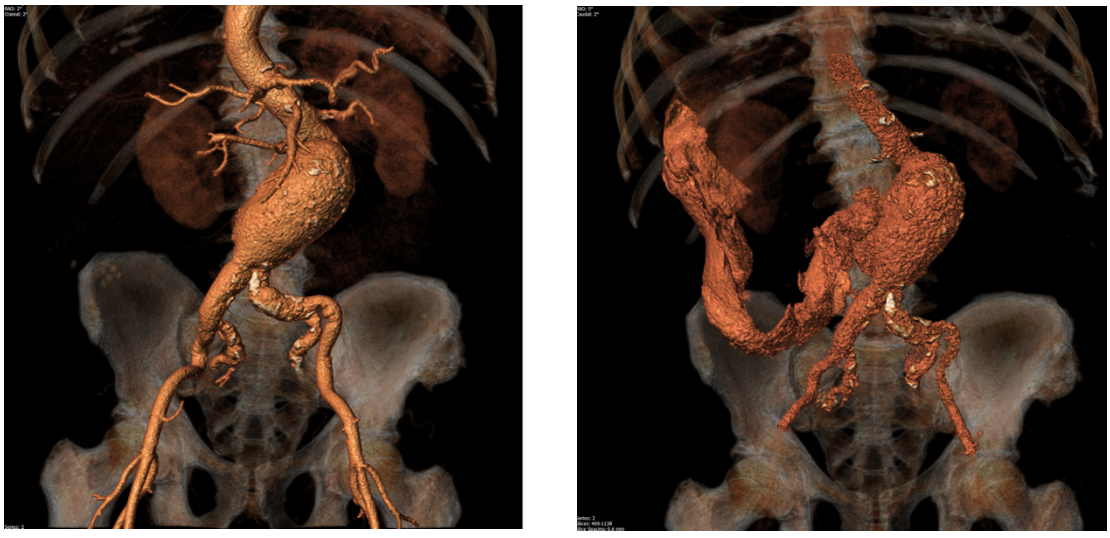

Figure III. Three-dimensional CT angio reconstructions of intact abdominal aortic aneurysm (left), and of the same aneurysm after rupture (right).

Unlike the iAAA that usually goes unnoticed by the patient, a symptomatic non-ruptured AAA presents with abdominal pain and palpable bulge in the umbilicus region but the aneurysm is not ruptured and hemodynamic instability is absent. A symptomatic AAA calls for prompt repair, however it is possible to await optimal conditions and resources for best surgical management and outcome.[19] The rAAA is different in its presentation from both intact and symptomatic AAA. It is accompanied by massive bleeding and possibly hemodynamic shock. The classic triad of symptoms for rAAA is abdominal pain, hypertension and a palpable pulsating mass in the abdomen although misdiagnosis of rAAA is still an issue for emergency departments and their personnel.[93]

2.4.1 Screening

Initiated in 2006, screening for AAA amongst 65-year-old males is now offered on a nationwide basis in Sweden. Reaching national coverage in 2015, the Swedish screening program offers a single scan to all 65-year-old men by a letter of invitation. Similar programs are in effect in both the United Kingdom[94] and in the US.[95] Screening for AAA in the United States is offered through different private and government programs directed at 65- to 75-year-old men with a history of smoking or a family history of AAA.[96] Contemporary data have demonstrated a reduction of AAA-specific mortality with screening as well as being cost-effective.[97, 98] In the Swedish screening program, to prevent one premature AAA related death, the number needed to screen is 667.[31] Furthermore, AAA-screening contributes to a lower all-cause mortality.[97] With a three- to four-fold increased risk in rupture in women[23], the implementation of female screening is debated but it has yet to prove reductions in rupture rates or economic viability.[99, 100]

2.4.2 Improving care of AAA patients

One might argue that no patient with a known AAA should rupture as surveillance protocols and intervention criteria are designed to minimize these events. With nationwide screening already implemented, more Swedish men with AAA will enter the offered surveillance program. Some patients themselves decline elective surgery, possibly due to the operative risk assessment. However, when rupture occurs, a proportion of these still undergo emergency repair with much higher mortality and complication rates. Identifying the proportion of previously diagnosed AAA amongst patients with a ruptured AAA is a possible gateway into finding new areas in need of improvement in the overall care of the AAA-patient. Some patients are deemed unfit for surgery at time of initial AAA-diagnosis; this number has been reported

to be around 11–27 % of patients with an AAA.[101, 102] Proper risk assessment is imperative in the preoperative phase.[103] It has been suggested to use different risk score models in assessing operative risk[104, 105] and incorporating these results when discussing surgical risk with the patient.[19]

2.4.3 Non-operative management of rAAA

Some patients admitted to a hospital with rAAA are deemed unlikely to survive surgical repair and are managed conservatively i.e. palliation. The acute setting of rAAA demands quick decisions and surgical judgment which is not always an easy task. Scoring systems are sometimes proposed as an aid in the decision making, but these have not proven sufficient or accurate.[106] Recent studies have implied that repair of rAAA in patients >80 years old could give acceptable results.[107-109] Following current recommendations by the European society for vascular surgery, decisions on non-operative management should not be based solely on scoring systems or on advanced age.[20] A great variation in turn-down rates for rAAA patients exists.[56, 70, 83, 108, 110, 111]

2.5 TREATMENT

2.5.1 iAAA. Medical treatment and preoperative optimization

Several drugs have been studied in an effort to find pharmaceutical treatment of aneurysm growth and for prevention of rupture. These include Doxycycline, Metformin, β-receptor blockers, ACE-inhibitors and fluoroquinolones among others.[112, 113] Although studies in animal models or ex vivo human AAA tissue have implied possible associations, none has proven beneficial in clinical trials[112, 114] except in an observational propensity-score matched analysis of fluoroquinolones.[113] The true effect of this drug on AAA growth and rupture remains in debate, however. With the known strong association between smoking and aneurysm growth, smoking cessation should be recommended to all AAA patients.[24, 33, 115] Optimizing overall cardiac, pulmonary and renal function is imperative to achieve good postoperative results. Although the level of evidence is low, statins are used to reduce the incidence of major cardiovascular events following surgical repair[50, 116, 117] but not suggested to reduce the risk of AAA expansion and rupture.[19] Antiplatelet therapy is recommended for AAA according to European guidelines[20] but the same recommendation is not presented by the American Society

for vascular surgery.[19] There is a lack of randomized trials investigating the effect of antiplatelet therapy specifically on AAA-patients, nonetheless it is used in a more pragmatic matter to reduce cardiovascular events during the peri- and postoperative period.[118]

2.5.2 rAAA. Initial management

The rAAA is a lethal condition and non-repair is associated with an almost certain death. The only treatment is surgical repair and the methods and outcome after repair is presented below. A limitation often seen in large randomized trials or cohort studies is the lack of representation of the proportion not treated at time of rupture diagnosis.[70, 71] Also, the fact that those never reaching the hospital, dying at home with often no autopsy conducted are not taken into account hinders epidemiological conclusions.[57] A Finnish study from 2016 reported on 27.5 % of their rAAA patients dying out-of-hospital and 43.2 % undergoing surgery.[71] Furthermore, *mors in tabula* in patients with rAAA is a source of misclassification as they may not be registered properly in vascular registries or in-hospital records.

2.5.3 Surgical intervention

Open repair (OR) has been in practice since the 1950s.[2] The procedure, performed under general anesthesia includes a large midline laparotomy, replacing the aneurysmatic aorta with interposition of a graft, excluding the aneurysm from the blood flow. Although improvements in surgical outcome after this high-risk procedure has been made, it was not until endovascular aortic repair (EVAR) was introduced in the early 1990s[5, 6] that the first real competitor for the title of gold standard for treating AAAs arrived. By inserting an endograft through a transfemoral-approach using the Seldinger-technique and assisted by perioperative imaging, the patient's AAA is excluded from the blood flow with minimal surgical trauma and often under local anesthesia, *figure IV*.

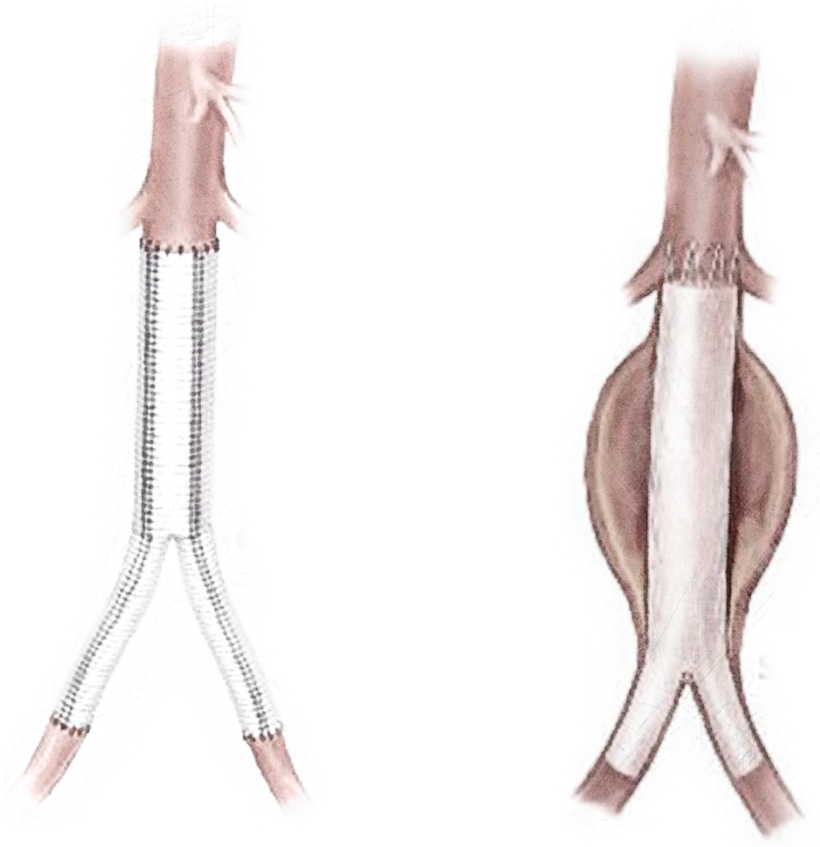

Figure IV. Images of final result after open repair (OR, left) and endovascular aortic repair (EVAR, right). Note that after EVAR, the aneurysm sac is still intact and left as is with risk of further enlargement and rupture despite being treated.

Today, in a modern elective clinical setting, most patients are assessed for both types of repair and recommended the most suitable modality based on radiological findings of aneurysm anatomy and the patient's co-morbidity status.[115] A preoperative CT scan indicates if EVAR is feasible using different anatomical measurements including aneurysm neck, angulation and proximity to visceral arteries. In the Western world, trends shift between OR and EVAR. The Swedish vascular registry (SWEDVASC) reports annually on frequencies of repair types for AAA. In the report on the 2017 data it was apparent that EVAR is becoming more used in both the elective and acute settings. In 2017, EVAR was used in 59 % of AAA cases, compared to 47.6 % in 2009. For rAAA the proportion of EVAR was 45.9 % in 2017 compared to 22.5 % in 2009.[119] EVAR has increasingly become the first hand choice for treating patients with AAA and although less common in the ruptured setting, some centers have declared an EVAR-first strategy even

when a patient presents with a rAAA.[120, 121] Unlike after OR, where follow up is often limited to a 30-day or one-year visit to the out-patient clinic, EVAR-patients are monitored through regular imaging with ultrasound or CT-scans to detect possible unfavorable graft dislocations or migration as well as possible aneurysm sac expansion that ultimately can lead to a late rupture.[122, 123]

2.6 OUTCOME

2.6.1 Outcome of surgical intervention in iAAA

In Sweden the 30-day mortality rate in 2017 after repair for iAAA was 1.0 % and 2.1 % for 90-day mortality.[119] There are four large RCTs providing modern comparisons on outcome between OR and EVAR, table II. These studies have randomized patients with iAAA to OR or EVAR. Short term results have been in favor of EVAR; including shorter total hospital stay[124] and reduced early complication rates as well as low early mortality.[125-127] However, these early gains do not seem to hold up as long-term results are reported. The EVAR 1 trial, carried out in the United Kingdom during a four-year period from 1999 to 2003, included patients deemed eligible for EVAR and randomized to either conventional OR or EVAR. Their short-term results showed 1.7 % 30-day postoperative mortality for the EVAR compared to 4.7 % in the open repair group.[126] The long-term outcome was recently published where the benefits of short-term outcome of EVAR was overshadowed by its inferior late survival partly due to secondary sac rupture (7 %) in the EVAR group.[123] The American OVER-trial found the same results, with EVAR proving superior in short-term mortality but equal in its long-term mortality results after three years.[128, 129] Furthermore, in their nine-year follow up study, neither survival, quality of life, costs or cost-effectiveness differed between OR and EVAR groups. However, their initial study did show other benefits with EVAR in the perihospital-period such as reduced procedure time, less transfusion requirements and shorter hospital stay. Unlike these other RCTs, the French *Anevrysme de l'aorte abdominale: Chirurgie versus Endoprothese* (ACE) trial found no early or late survival benefits with EVAR[130] but did report on a higher re-intervention rate in the EVAR group (16 % versus 2.4 %). With these studies it is important to be aware of the generalizability or rather the lack of it, in interpreting the results. The proportion of women in the trials is often low, selection bias is an important factor for error, as well as differences in follow-up time between the RCTs, table II.

The EVAR 2 trial, designed to include patients deemed unfit for OR, investigated whether EVAR was superior to best medical treatment in these patients. Although it showed EVAR contributing significantly to a lower rate of aneurysm-related mortality, no overall survival benefit with EVAR compared to no intervention was found and EVAR was associated with increased costs due to continued surveillance and interventions.[131] The long-term data from this trial further strengthens these results.[132] Furthermore, <40 % of the studied patients were alive after four years and <10 % of the patients were alive after twelve years, regardless of EVAR or not, concluding that the majority of EVAR-2 patients had a limited life expectancy.

Table II. Randomized controlled trials investigating outcome for iAAA after EVAR versus OR.

			30-day mortality		Long-term** mortality	
	No of patients	% Male	EVAR	OR	EVAR	OR
EVAR 1[123, 126]	1252	90.5 %	1.7 %	4.7 %	53 %	46 %
OVER[128, 129]	881	99.3 %	0.5 %	3.0 %	32.9 %	33.4 %
ACE[130]	316	99 %	1.3 %*	0.6 %*	17.6 %	14.9 %
DREAM[127]	351	91.7 %	1.2 %*	4.6 %*	31.1 %	30.1 %

* In-hospital mortality

** Long-term was defined differently in the studies. EVAR 1: 6904 person-years follow-up, OVER: Three year follow-up, ACE: Three year follow-up (median, range 0–4.8), DREAM: 6.4 years (median) follow-up.

2.6.2 Outcome of surgical intervention in rAAA

In Sweden, the 30-day mortality rate in 2017 after repair for rAAA, was 22.5 % and the 90-day mortality 28.7 %.[119] Three large randomized clinical trials have compared OR to EVAR with regard to outcome after intervention in rAAA, table III. The IMPROVE trial set in the United Kingdom (plus one center in Canada) included 613 patients randomized to endovascular strategy or OR. 30-day mortality was similar in both groups, with 35.4 % in the endovascular strategy group and 37.4 % in the OR group.[133] A one-year outcome analysis described no benefits in survival for either group but earlier discharge and better quality of life (QoL) in the

endovascular strategy group.[134] However, by three years EVAR was associated with a survival advantage but the improved QoL among EVAR patients was no longer as prominent.[135] The French ECAR-trial showed similar results as did the Dutch AJAX trial.[136] The AJAX trial demonstrated lower mortality rates than the other RCTs, possible due to optimization of logistics and centralized care in centers of expertise.[136]

Table III. Three randomized trials for determining which of the modalities of OR and EVAR have the best 30-day survival.

				30 day mortality	
Name of study	Type of study	No of patients	*% Male patients*	*OR*	*EVAR*
IMPROVE[133]	Multicentre	613	78.3 %	37.4 %	35.4 %
AJAX[136]	Three centers	116	85.3 %	25 %	21%
ECAR[137]	Multicentre	107	90.7 %	18 %	24 %

Regardless of the modality of repair, mortality rates are very high, especially compared to the mortality after repair of iAAA. Other than perioperative death due to massive hemorrhage and cardiac arrest, several postoperative complications contribute to these high mortality rates. These include multiple-organ failure, bowel ischemia, lower-extremity ischemia, cerebrovascular complications, renal failure and cardiopulmonary complications. A severe postoperative complication following rAAA repair is abdominal compartment syndrome (ASC). When intra-abdominal pressure increases to critical levels (>20 mmHG), the perfusion of intra-abdominal organs decreases and ASC arises. For the rAAA patient, many risk factors for developing ASC are present including hemoperitoneum, open abdominal surgery, acidosis, coagulopathy and high age.[138] Swedish contemporary data shows ASC occurring in 6.8–6.9 % of rAAA cases compared to 0.5–1.6 % after repair of iAAA[139] but internationally the rate of ACS after rAAA has been reported higher.[140] The effect on mortality is evident as the Swedish study demonstrated 30-day mortality rates at 42.4 % for treated rAAA patients who developed ASC and 23.5 % for those who did not.[139] Interestingly, EVAR rather than OR, has been associated

with lower in-hospital morbidity following repair of rAAA.[141] However this assumption is not fully established.[142]

2.7 SOCIOECONOMIC POSITION

2.7.1 What it is and how to measure it

Socioeconomic position (SEP) is a complex term with a broad and multifaceted definition, *figure V*. The influence of SEP on overall health and burden of disease has consistently been deciphered and depicted, especially in the fields of cardiovascular disease[143-145] and cancer treatment.[146-148] Stratifying SEP and health often depicts the rich and wealthy enjoying a healthier and disease-free life, while poor, non-educated individuals suffer from more overall illness. Even for children of parents with low SEP this difference has been observed.[149] To understand and correctly apply the meaning of SEP, one must first clarify the components of the term.

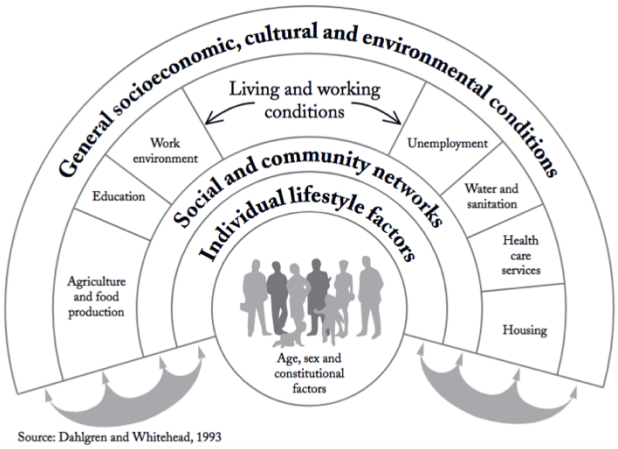

Figure V. The Dahlgren-Whitehead rainbow model maps the relationship between the individual, their social context and community and the overall social condition as determinants of health. The individual lifestyle is embedded in social norms and networks as well as living and working conditions and finally surrounded by general socioeconomic, cultural and environmental conditions.

2.7.2 Income

The most widely used indicator of SEP is income. Income is a quantitative measurement allowing for a straight, non-conceptual approach and analysis. Different assessment tools are used based on differences in available data between nations. Determining income on an individual or household basis is only possible in nations with population based registries on that level such as in the Nordic countries and Sweden in specific. When these data are absent, other nations turn to different index calculations, such as the neighborhood deprivation index, often

seen in US studies.[150] The relation between income and health has been attributed to both a material pathway – consumption of goods and health-promoting activities, and to a psychosocial mechanism where the relative social position of an individual relates to his or her heath status (even among the rich, the least rich feel poor and in that, they face worse health). One usually speaks of a social gradient, where the higher the income the better the health.[151] It has been suggested that this follows a curve-linear gradient showing that an increase in income has a higher effect in the low-income field while it has less effect for the already rich, *figure VI*.

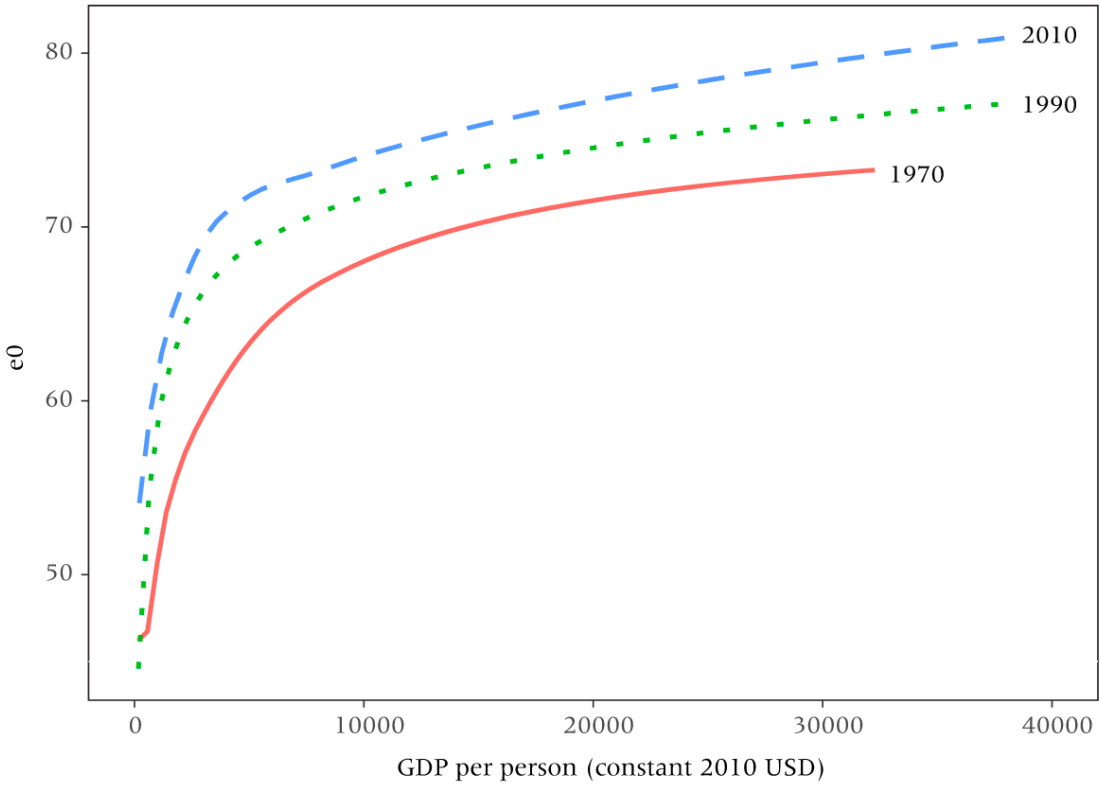

Figure VI. Example of a Preston curve. Here the difference in life-expectancy at birth is depicted, comparing data from 1970, 1990 and 2010 in the USA based on the Gross Domestic Product (GDP) per capita. (Source: Lutz W, Kebede E. Popul Dev Rev. 2018 Jun;44(2):343–361. doi: 10.1111/padr.12141. Epub 2018 Apr 14.)

2.7.3 Relationship status – it's complicated

Whether or not marital status is to be viewed as a SEP variable independent of income, the economic impact of two possible income sources is unquestionable. In the Swedish registries, it is possible to extract data on disposable household income, adjusted for household composition, taking into account marital or cohabiting status as well as any minors living under the same roof. This gives a more pinpoint determination of an individual's SEP, based on

income and household composition. However, the notion of living with a partner in contrast to living alone has its benefits of mental support, better compliance with medical advice and prescription drugs but also regarding overall mortality.[152, 153] This has been shown to be more evident among men than women.[154]

2.7.4 Level of education

A person's level of education is sometimes used as a surrogate for actual income or assumed SEP. A correlation between higher mortality and low educational level has been demonstrated in the US in cancer patients.[155, 156] Also, educational level has been used to evaluate smoking habits and a correlation between a decline in smoking habits and higher educational level has been shown.[157, 158] In 2016, the Public Health Agency in Sweden released its public health report stating that the difference in mean remaining survival years was 5.1 years longer for women and 5.7 years longer for men with higher educational level than for those with low educational level.[159] Also, while men with low level of education have seen their life expectancy increase over the past two decades, women in Sweden with low level of education have had the least increase in remaining life expectancy over the last 25 years.[159] Not only does low level of education impact health, it interacts with female sex and amplifies inequality.

2.7.5 Index and context

Neighborhood deprivation index is a tool developed to incorporate different aspects of SEP without data on an individual level.[160, 161] It includes many of the factors previously described and more; including racial ethnicity. One of the oldest index-scoring systems for deprivation is the Carstairs index.[162] It is based on four census indicators; low social class, lack of car ownership, overcrowding and male unemployment. This method has mostly been used in the United Kingdom and stands as a predecessor for newer census-based index systems. In 2012 the Vancouver Area Neighborhood Deprivation Index (VANDIX) was published. It is based on the weighted summation of seven socio-economic variables including proportions of educational level, home owners, single-parent families, as well as unemployment ratio and income.[161]

2.7.6 SEP and surgical outcome

In surgery, and vascular surgery in particular, the correlation between SEP and surgical outcome has been sparsely studied with heterogeneous results. An American study

investigated high risk surgical procedures and found higher rates of postoperative mortality amongst the elderly with a lower SEP.[163] A recent Dutch study including different types of vascular interventions demonstrated that the severity of the AAA disease (i.e. rAAA as opposed to iAAA) increased with lower SEP and that survival was most affected by SEP in the lowest income regions.[164] Furthermore, a study from New Zealand investigated differences in outcome after AAA repair based on SEP and ethnic groups. Their results indicated both low SEP and being Maori as predictors of increased risk for postoperative mortality following AAA repair.[165] Just recently, a study from the United States demonstrated an association between SEP and long-term mortality after repair for iAAA. [150]

The pathway mediating the association between SEP and health outcomes has been described using several theoretical models. Different entry points for the impact of SEP on health, both on an individual and a society level have been suggested, *figure VII.*[166] To clarify parts of this model: social stratification can be seen as a reflection of how individuals aspire to reach higher social positions created by society, for instance through education. Differential exposure indicates that the exposure to different risk factors is dependent on the social position of the individual, such as work environment, *figure VII*. Depending on the SEP, individuals differ in their vulnerability against disease (differential vulnerability) and also in what consequences a disease has on the individual (differential consequences), *figure VII*.

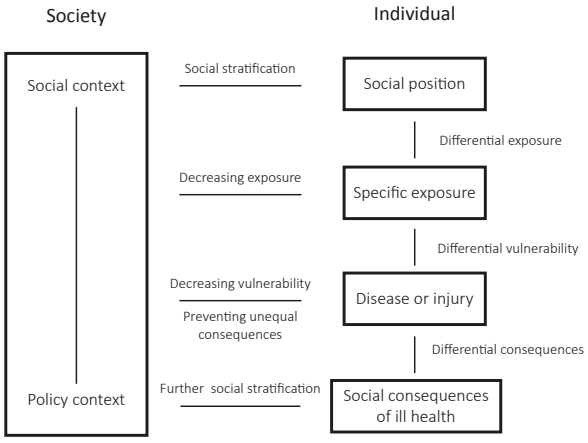

Figure VII. An overview of central mechanisms (to the left) and their associated policy entry points (center) related to social inequality in health. (*Source: Diderichsen et al*[166]). To explain this figure further, imagine a male individual with the lowest SEP. His SEP will expose him to risk factors for disease such as smoking, bad working environment etc (differential exposure). Furthermore his low SEP might allow him to fall ill more easily than others (differential vulnerability) and having to refrain from work will have greater economic consequences for him (differential consequences). Regulations can be performed on different levels to reduce these differential variables. For instance, regulations against smoking or harsh work environments (decreases exposure), providing free and easy accessible health care (decreases vulnerability) and offering regulated sick-leave and rehabilitation support (preventing unequal consequences).

2.8 LET'S TALK ABOUT SEX

The difference between the sexes in terms of disease onset, pathophysiology, progress and outcome is often debated within the field of AAA disease. AAA is considered a male-dominated disease with 4–6 times higher prevalence in men than in women. In a meta-analysis of the current prevalence of screening-detected AAA in women, the prevalence ranged from 0.31 percent to 1.53 percent[167]. The conundrum with AAA in women comes in five main points. Firstly and secondly, (i) the risk of rupture is three times higher in women than in men[44], (ii) women have a tendency to rupture at a smaller aneurysm diameter.[80, 85] The increased rupture risk is sometimes credited to peak wall stress or aortic tensile strength as well as to differences in collagen cross-linking in the aortic wall.[63, 168, 169] One explanation of the smaller aneurysm diameter among ruptures in women is that the ratio of aneurysm diameter to body surface area, (ASI), is higher at time of rupture in women than in men despite actual smaller aneurysm diameter.[80, 170, 171] It has even been proposed that the supposed male predominance in AAA prevalence is due to body size differences and adjusting for this would leave only small sex differences in AAA prevalence.[81] Thirdly, (iii) the median growth rate in women has been shown to be almost twice that in men independent of initial aneurysm size and age[172], though this has been contradicted in other studies.[39] Fourth, (iv) women have been shown to undergo repair at time of rupture less often[85] with higher age and more comorbidities in women influencing these results.[173] Finally, (v) it has been suggested that postoperative mortality after rAAA is higher in women compared to men, though these results are controversial and not homogenous.[83-85, 174, 175] Part of the uncertainty in these results is the lack of women included in most large studies of iAAA and rAAA.

2.9 MAPPING THE UNCHARTED TERRITORIES

With all this knowledge already at our disposal, what areas of the rAAA remain to be further explored? The main effort must lie in continuing to reduce the rAAA incidence. Screening and smoking cessation will most likely be the two greatest steps in this direction; by finding the AAA before it ruptures with the former, and by reducing aneurysm formation and growth through the latter. However, there are other aspects of rAAA that need to be addressed. We know that many ruptures occur in patients with known aneurysms. Why are they allowed to rupture? Is it solely due to the patients being denied elective repair or have they actively declined that

option? Are there other, modifiable, reasons behind these ruptures? If SEP plays a role in severity of illness and mortality, maybe these groups need specific and targeted efforts both pre- and postoperatively to ensure improved overall health even in the socioeconomically deprived. RCTs in rAAA have a low proportion of women included and conclusions on sex differences in outcome are therefore difficult to reach. Using large retrospective cohort data gives a higher volume of women in these studies but the level of evidence is low due to risk of unadjusted confounders and both type I and type II errors. However, using a statistical method that aims to imitate a RCT while using retrospective observational data could possibly bridge the gap between the known and unknown aspects of sex differences in AAA-disease.

3 AIMS OF THE THESIS

The overall aim of this thesis was to study aspects of rAAA epidemiology and improve our knowledge of rAAA disease with special focus on some of the more vulnerable groups in society prone to suffer more from inequality in health care.

The specific aims were:

STUDY I. To investigate the contemporary care of all treated and untreated patients with rAAA admitted to a hospital, with special consideration to age and gender.

STUDY II. To investigate the proportion of previously known AAA among patients presenting with rupture and to present reasons for non-repair at initial time of iAAA diagnosis.

STUDY III. To study long-term trends in incidence and management of rAAA and to compare the SEP distribution in patients with iAAA and rAAA. A particular aim was to elucidate the influence of SEP on type of index diagnosis at presentation (iAAA or rAAA) and on the outcome after rAAA repair.

STUDY IV. To investigate sex differences in repair rates and repair outcomes in rAAA patients.

4 DATA SOURCES AND METHODS

4.1 OVERVIEW

Table IV. Presentation of material and methods used in Studies I–IV.

	Study I	Study II	Study III	Study IV
Study design	Population-based, retrospective	Population-based, retrospective	Population-based, retrospective	Population-based, retrospective
Data sources	Hospital charts, SWEDVASC	Hospital charts	Swedish NPR, Swedish Cause of Death Register, LISA	Swedish NPR, Swedish Cause of Death Register, LISA, SWEDVASC
Population	Inhabitants of Counties of Stockholm and Gotland	Inhabitants of Counties of Stockholm and Gotland	All inhabitants in Sweden	All inhabitants in Sweden
N*	283	283	41,222	10,724
Time period	2009–2013	2009–2013	2001–2015**	2001–2015
Exposure	Repair	rAAA	SEP	Sex
Outcome	Repair rates, Sex-inequality	Rate of previously known AAA	Time trends in incidence, repair modality, mortality. Index diagnosis rAAA. Outcome after repair	Repair at time of rupture. Repair modality. Outcome after repair
Statistical method	Frequency distribution and relative proportions	Frequency distribution and relative proportions	Frequency distribution and relative proportions. Logistic regression	Propensity-score matching

*Abbreviations: NPR National Patient Register, LISA Longitudinal integration database for health insurance and labour market studies (extracted from Statistics Sweden), rAAA ruptured abdominal aortic aneurysm, AAA abdominal aortic aneurysm, SEP Socioeconomic position. *N=Total number of included individuals in the study. **Data from 1995–2000 was also extracted to provide a 5-year diagnosis-free interval 1995–1999. The year 2000 was excluded as we included disposable household income from the previous year of diagnosis.*

4.2 DATA SOURCES

Different registers have been used within the scope of this thesis and the included studies.

4.2.1 The Swedish National Patient Register

The Swedish National Patient Register (NPR) is composed of several registers including the Inpatient register, also known as the Hospital Discharge Register, and the Outpatient Register. It was started in 1964 and reached complete coverage by 1987. The mandatory nature of the register for all physicians, public and private, to deliver data to the register has led to a 99 % coverage of all somatic and psychiatric discharges. The register uses current ICD-codes for registration of both primary and secondary diagnosis and also includes mode of discharge, i.e. to where the patient was discharged. Each hospital discharge is keyed to the individual's Personal identity number (PIN) allowing easy overview and cross-matching of all entries in the register for a specific individual. Although the In-patient register has an almost complete coverage, the Out-patient register has a coverage of around 80 % as it does not include all private care-givers (for public care-givers the coverage is close to 100 %). In Sweden, all vascular surgery procedures except venous interventions are only provided through public care-givers. An external validation of the NPR from 2011 describes its positive predictive value at 85–95 %.[176]

4.2.2 The Swedish Cause of Death Register

The Swedish Cause of Death Register (CDR) is managed by the National Board of Health and Welfare (NBHW) and includes data on all deaths among Swedish residents, domestic and abroad covering 99 % of Swedish residents. The basis for the register is the death certificate (*dödsorsaksintyg*), issued by the physician last seeing the patient and must be submitted within three weeks of the death. Before this, a notification of death (*dödsbevis*) must be issued immediately to the Swedish Tax Agency. Information from both these are recorded in the CDR. The death certificate includes the underlying cause of death; primary, secondary and so on. The quality of the register is said to be mainly affected by two factors; the quality with which the physician certifies the death and the quality in processing the death certificates and validating the data.[177] The Cause of Death Register also couples the PIN of the individual with the data in the register allowing for cross-matching between different registers. Some have suggested that the decrease in autopsy rate in Sweden, from 50 % in the 1970s to between 7–

15 % in 2014 has had a negative effect on the quality of the register. However, with the increased use of modern laboratory and imaging tools, more accurate diagnostics preceding the death ought to combat such deterioration.[178]

4.2.3 The Swedish Vascular Register

The Swedish Vascular Register (SWEDVASC) was started in 1987 and has grown to become a nationwide register with an excellent external and internal validity.[179] This being said, the specific reporting on rAAA might be the most uncertain variable, as the acute nature of the disease might prompt intervention at non-SWEDVASC affiliated hospitals and misclassification due to *mors in tabula*. This would lead to an underestimation of the postoperative mortality rates from SWEDVASC. Although in its previous forms the register lacked nationwide coverage and a heavy manual paper-based registration process impaired the reporting rates, it is now, in its electronic form a widely used register for all vascular surgeons in Sweden. The reporting to SWEDVASC is, however, not mandatory from a legal or reimbursement aspect. Only treated patients are registered in SWEDVASC. Pre-, peri- and postoperative data is registered including data on comorbidity, smoking, height and weight of the patient, type of repair, type of anesthesia, postoperative complications as well as postoperative mortality. Beyond these, also QoL and Patient Reported Outcome Measures (PROM) are registered for some procedures.

4.2.4 Longitudinal integration database for health insurance and labour market studies (LISA)

The LISA database is managed by Statistics Sweden (*Statistiska centralbyrån)* and since its start in 1990 the database is annually updated with data from the labour market, educational and social sectors. Data is individually registered but connections to family and places of employment are also available. Among other data, disposable income, highest level of education, country of birth and place of residence are some of the data available from LISA. The PIN-specificity of the database allows for cross-matching with other registers from other register holders.

4.3 METHODS

Study I and II. Participants were identified using local hospital records. The ICD-code I73.1 was used to identify rAAA cases. A chart review was performed of each included case and data on sex, repair, repair type, comorbidity and outcome after repair was extracted. The rAAA was verified through imaging, at intervention or in autopsy reports. For Study II a chart review was performed of each included case and data on previously diagnosed iAAA was extracted, as was the reason for non-repair at time of initial iAAA diagnosis.

Study III. Data from the NPR and CDR was extracted for the first registered index diagnosis of either iAAA or rAAA. Data on disposable household income (divided into quintiles of increasing income Q1–Q5), and level of education was extracted and matched from Statistics Sweden and used as markers of SEP. Data on age, sex and comorbidities as well as time of death was also extracted and included in the analysis. Logistic regression was performed to assess the association between SEP and the outcome events. For analysis of time trends, a Mantel-Haenszel test for trend was performed. Analysis for missing data >5 % was proceeded with multiple imputation by chained equations.

Study IV. The NPR and CDR were scanned for all cases of rAAA during 2001–2015. Data on SEP was extracted from Statistics Sweden and cross-matched. Data on age, sex, year of rupture and comorbidities as well as time of death was also extracted and included in the analysis. Similarity between subjects is based on estimated treatment probabilities, known as propensity-score (PS). The treatment effect is computed by taking the average of the difference between the observed and potential outcomes for each subject. Matching was performed with a 1:3 ratio; each female was matched to the nearest three male individuals if the distance between the PS of these individuals was no greater than 0.08 (caliper). Average treatment effect (ATE) was calculated in this model. For a subgroup analysis on postoperative mortality, including postoperative complications in our PS-model, patients from 2009–2015 were included and the caliper was raised to 0.15.

4.4 ETHICAL CONSIDERATIONS

All studies in this thesis were approved by the Regional Ethical Review Board in Stockholm. For Study I and II, the nature of the rAAA disease made informed consent from the subject impossible. All data was initially created anonymously with a link between the data and the PIN stored according to the rules and regulations provided by Karolinska Institutet. All the data for Study I and II was presented at a group level. For Study III and IV, the linking of data on an individual between registers was performed by the NBHW before the data was anonymously handed over to our research group making a reverse identification impossible.

5 RESULTS AND DISCUSSION

5.1 RESULTS

Study I and II. These two studies included 283 individuals with rAAA. Three out of four patients were male (n=214; 76 %). Mean age of the whole cohort of patients was 78.7 ± 8.9. Women were older (82 vs 78 years, p<.001), had smaller AAA diameter (74 vs 83 mm, p=0.006) and lower BMI (22.4 vs 28.4, p=0.002) compared to men. **Study I** found no difference between the sexes in repair rates or the use of EVAR. No difference was noted in postoperative mortality. A high proportion of patients admitted to a hospital with rAAA, (75 %) underwent repair, *figure VIII*.

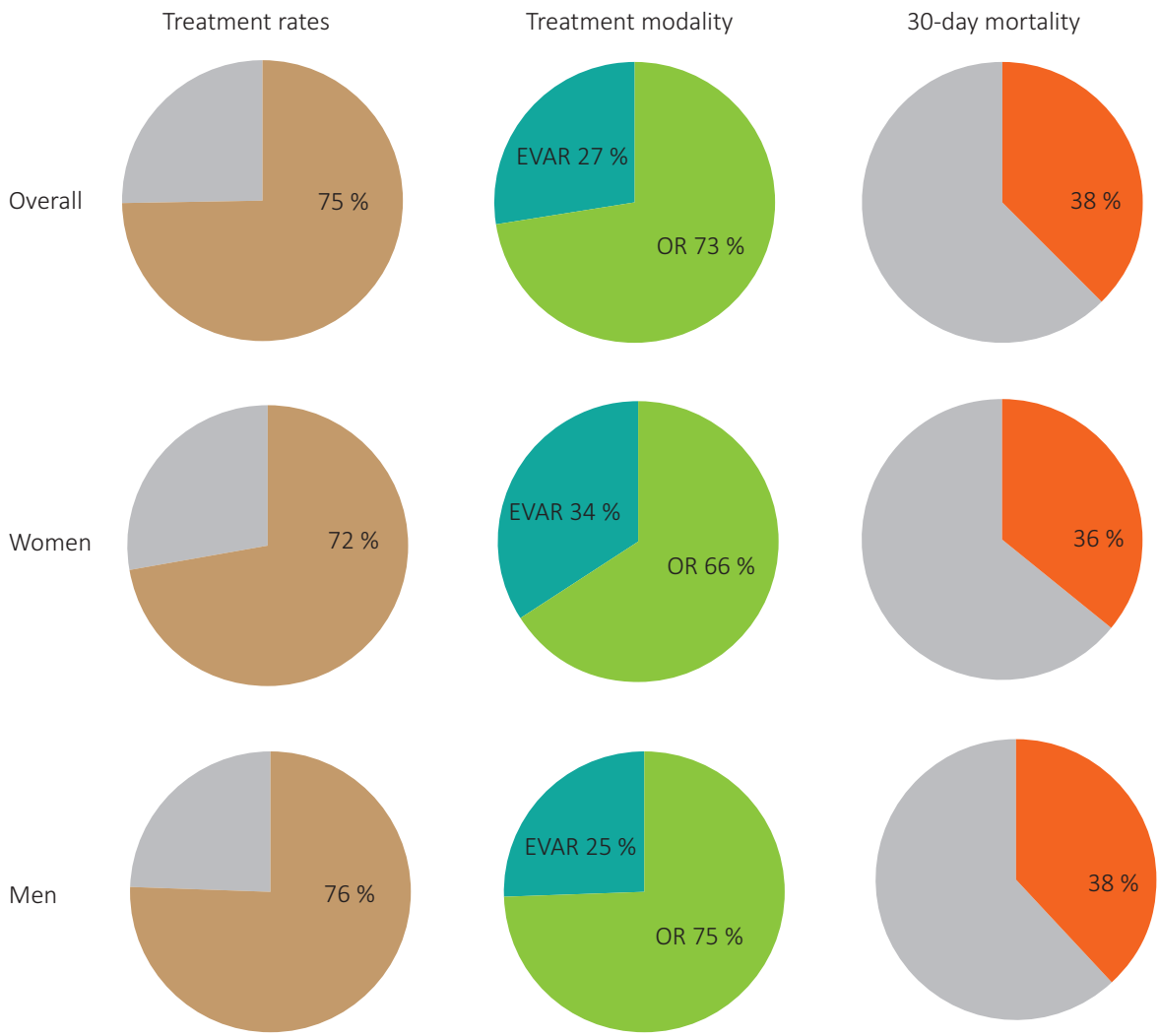

Figure VIII. All admitted patients with rAAA (n=283), their repair rates (brown), modality of repair (green) and mortality within 30 days after repair (red).

Study II showed that the proportion of previously detected aneurysm was 30 % (n=85). Four principal reasons for the decision not to treat at the time of aneurysm detection were identified: denied elective surgery due to comorbidity/high age (n=31); missed surveillance (n=26); patients' choice (n=15); denied elective surgery due to aneurysm size (n=11). In two cases the reason for non-repair or inadequate surveillance was not clear, *figure IX.*

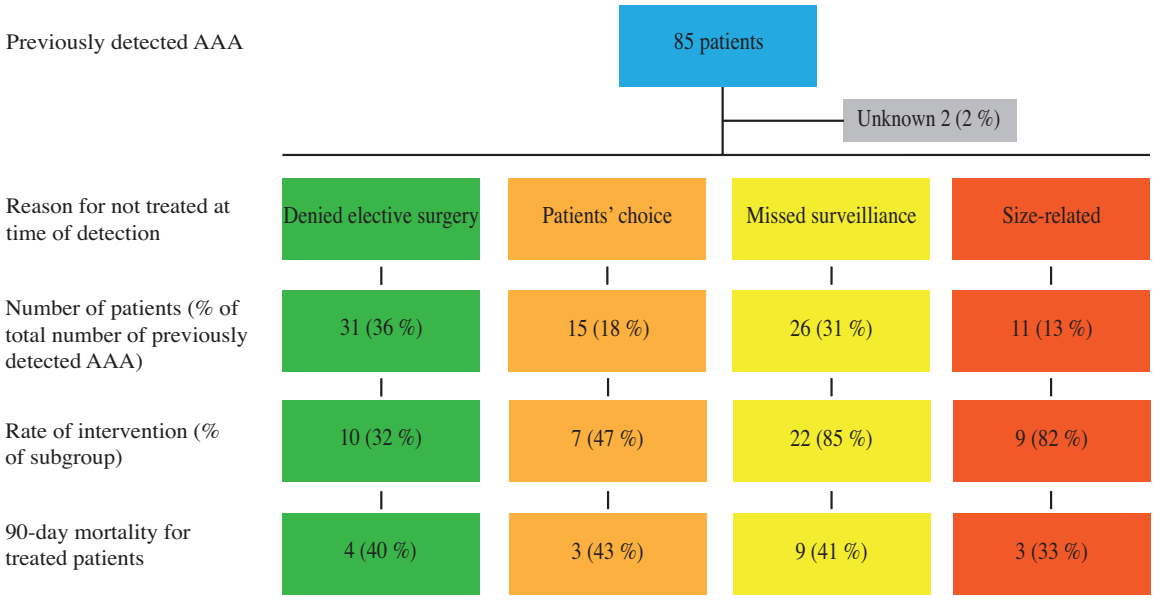

Figure IX. Chart overview of individuals with a previously known abdominal aortic aneurysm (AAA) among rAAA patients and reasons for non-repair at initial AAA diagnosis.

Study III. From 2001 to 2015, a total of 41,222 individuals were diagnosed with either an iAAA (n=33,254; 80.7 %) or a rAAA (n=7,968; 19.3 %) and included in the analysis, table V. The overall proportion of women was 21.7 %. The incidence of iAAA per 100,000 inhabitants aged >45 years peaked from 45.9 in 2001 to 73.5 in 2011 and later dropped to 51.4 in 2015. Time trends showed a steady decrease in the absolute number of cases of rAAA, from 2,505 in the earliest time-period to 1,679 in the latest (p<.001), *figure X.* The use of EVAR increased, especially during the last 9 years (2007–2015), *figure X*. During the study period, postoperative survival after repair for rAAA improved and the study population had an increase in mean age from 75.7 in 2001 to 78.6 in 2015 (p<.001).

Table V. Demographics of included individuals (n=41,222) in **Study III**, presented in quintiles of disposable household income; Q1 representing the poorest and Q5 the richest quintile.

	All n=41,222	Q1 n=8,244	Q2 n=8,245	Q3 n=8,244	Q4 n=8,245	Q5 n=8,244
Patient demographics						
iAAA (n; %)	33,254 (80.7)	6,009 (72.9)	6,358 (77.1)	6,602 (80.1)	6,957 (84.4)	7,328 (88.9)
rAAA (n; %)	7,968 (19.3)	2,235 (27.1)	1,887 (22.9)	1,642 (19.9)	1,288 (15.6)	916 (11.1)
Mean age (SD)	73.7 (8.6)	76.4 (8.7)	76.2 (8.0)	74.8 (8.0)	72.0 (8.3)	69.0 (7.7)
Women (n; %)	8925 (21.7)	2,668 (32.4)	2,409 (29.2)	1,838 (22.3)	1,162 (14.1)	848 (10.3)
Women with rAAA (n;%)	1862 (20.9)	723 (27.4)	524 (21.8)	329 (17.9)	174 (15.0)	112 (13.2)
Comorbidity						
Diabetes (n; %)	4,330 (10.5)	700 (8.5)	907 (11.0)	953 (11.6)	952 (11.6)	818 (10.0)
Hypertension (n; %)	16,307 (39.6)	2,507 (30.4)	3,216 (39.0)	3,611 (43.8)	3,565 (43.2)	3,408 (41.3)
Hyperlipidemia (n; %)	6,190 (15.0)	694 (8.4)	1,021 (12.4)	1,403 (17.0)	1,514 (18.4)	1,558 (18.9)
COPD (n; %)	4,574 (11.1)	887 (10.8)	1,125 (13.6)	1,069 (13.0)	841 (10.2)	652 (7.9)
Stroke (n; %)	4,381 (10.6)	904 (11.0)	992 (12.0)	986 (12.0)	850 (10.3)	649 (7.9)
Renal failure (n; %)	1562 (3.8)	299 (3.6)	363 (4.4)	359 (4.4)	315 (3.8)	226 (2.7)
Heart disease (n; %)	8,951 (21.7)	1,470 (17.8)	1,782 (21.6)	2,018 (24.5)	1,963 (23.8)	1,718 (20.8)
Malignancy (n; %)	7,331 (17.8)	1,141 (13.8)	1,451 (17.6)	1,664 (20.2)	1,583 (19.2)	1,492 (18.1)
Level of education*						
Low (up to 9 years)	16998 (48.0)	3,387 (65.0)	4,219 (52.3)	3,975 (52.3)	3,142 (40.1)	2,275 (28.6)
Middle (10-12 years)	13571 (38.3)	1,535 (29.4)	2,215 (38.6)	2,936 (38.6)	3,432 (43.9)	3,453 (43.3)
High (>12 years)	4845 (13.7)	292 (5.6)	364 (9.1)	695 (9.1)	1,254 (16.0)	2,240 (28.1)

*Abbreviations: iAAA: intact abdominal aortic aneurysm, rAAA: ruptured abdominal aortic aneurysm, SD: standard deviation, COPD: chronic obstructive pulmonary disease, *5808 missing cases. Of individuals with a rupture at index-event, 2,187 had missing information on level of education. Of those receiving repair, 494 individuals had missing data on level of education.*

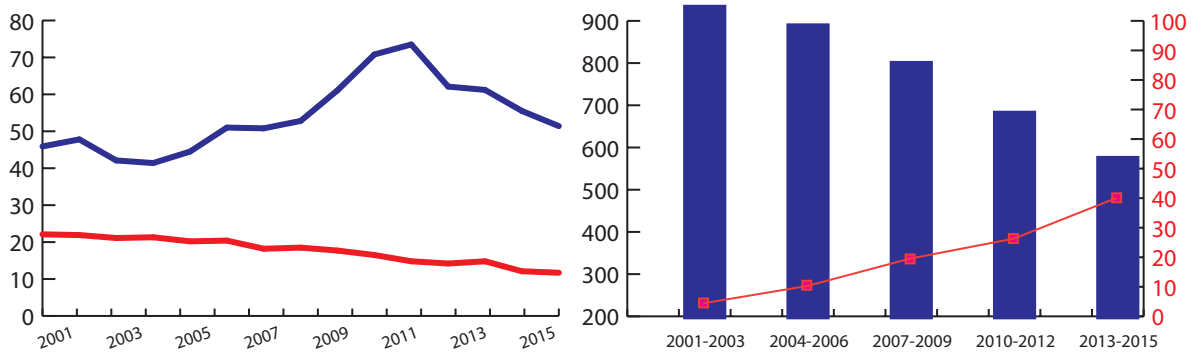

Figure X. To the left, annual incidence (x-axis) of intact abdominal aortic aneurysm (iAAA) (blue line) and ruptured AAA (rAAA)(red line) per 100,000 inhabitants aged ≥ 45. Screening for iAAA was initiated in 2006. Nationwide coverage was achieved in 2015. To the right**,** annual number of treated rAAA per time-period (blue staples, left axis) and the percentage treated with endovascular aortic repair (EVAR) (red line, right axis).

A higher risk of presenting with a rAAA at time of index diagnosis was found for both low disposable household income and low level of education, table VI. After adjusting for age, sex and comorbid conditions, the association remained; OR 2.16 (95 % CI 1.98–2.36, p<.001) for Q1 and OR 1.33 (95 % CI 1.21–1.46, p<.001) for low level of education. Overall one-year mortality in rAAA patients was 76.5 % (6,096 of 7,968). Low disposable household income (Q1 and Q2), adjusted for sex, age and comorbidities was associated with increased one-year mortality after rAAA repair; OR 1.49 (95 % CI 1.13–1.97, p=0.005). Low educational level did not influence survival after rAAA repair, table VI.

Table VI. Associations between socioeconomic position indicators and presenting with ruptured, as opposed to intact abdominal aortic aneurysm as index-event and 90-day mortality after repair for ruptured abdominal aortic aneurysm (rAAA).

	rAAA as index diagnosis *(n=7,968)*			90-day mortality (*n=1,103*)		
	Adjusted*			Adjusted*		
	OR	95 % CI	*P*	OR	95 % CI	*P*
Disposable household income						
Q1	2.98	2.74–3.24	<.001	1.42	1.07–1.89	0.014
Q2	2.37	2.18–2.59	<.001	1.36	1.03–1.80	0.031
Q3	1.99	1.82–2.17	<.001	0.99	0.74–1.31	0.923
Q4	1.48	1.35–1.62	<.001	1.07	0.80–1.43	0.661
Q5	ref	ref	ref	ref	ref	ref
Level of education						
Low (up to 9 years)	1.52	1.38–1.68	<.001	1.31	0.98–1.76	0.068
Middle (10–12 years)	1.12	1.02–1.22	0.023	1.22	0.89–1.66	0.210
High (> 12 years)	ref	ref	ref	ref	ref	ref

*Abbreviations: rAAA: ruptured abdominal aortic aneurysm, OR: odds ratio, CI: confidential interval, ref: reference. *Adjusted for sex, age (as a continuous variable) and comorbidity (Diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disorder, stroke, heart disease, renal failure, malignancy).*

Study IV.

A total of 10,724 individuals with rAAA were identified and included in the study, a minority were women (n=2,622, 24.4 %). The majority (n=8,498, 79.2 %) were found through the NPR, while the remaining 2,226 individuals (20.8 %) were found in the CDR.

In the complete sample of 10,724 individuals, the association between female sex and not receiving repair reached significance with an ATE of -0.08 (95 % CI -0.106 – -0.055, p<.001).

These differences remained even after excluding individuals from the CDR register. The PSM model with the treated patients only (n=4,480) and EVAR as outcome was not significantly different between the sexes (ATE=-0.022, 95 % CI -0.049–0.005, p=0.109). Treated women had a higher postoperative mortality than men at 30 days, 90 days and 1 year, (ATE ranging from 0.086–0.095), table VII.

Table VII. Average difference in outcomes between sexes after propensity-score-matching.

Outcome	Propensity-score-matched analysis on entire sample n=10,724		
	ATE	95 % CI	P
Treated	-0.08	-0.106 – - 0.055	<.001
	Propensity-score-matched analysis on in-patients only n=8,498		
	ATE	95 % CI	P
Treated	-0.089	-0.119 – -0.060	<.001
	Propensity score matched analysis on treated sample n=4,480		
	ATE	95 % CI	P
EVAR	-0.022	-0.049–0.005	0.109
	Propensity score matched analysis on treated sample n=4,480		
	ATE	95 % CI	P
30d mortality	0.094	0.053–0.135	<.001
90d mortality	0.086	0.043–0.128	<.001
One-year mortality	0.095	0.052–0.137	<.001

Propensity-score was calculated with the inclusion of the following covariates; age (as splines), year of diagnosis, diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD), renal failure, ischemic heart disease, cancer and SEP. For the last model, EVAR was added as a variable for the propensity-score calculation.

While male rAAA incidence declined rapidly, female incidence rates remained constant. After dividing the sexes into age-groups (<65, 65–74, 75–84 and >84 years), the time trends showed a steep decline in men aged 65–84 years, *figure XI*. Postoperative mortality declined over time but overall mortality did not, *figure XII*.

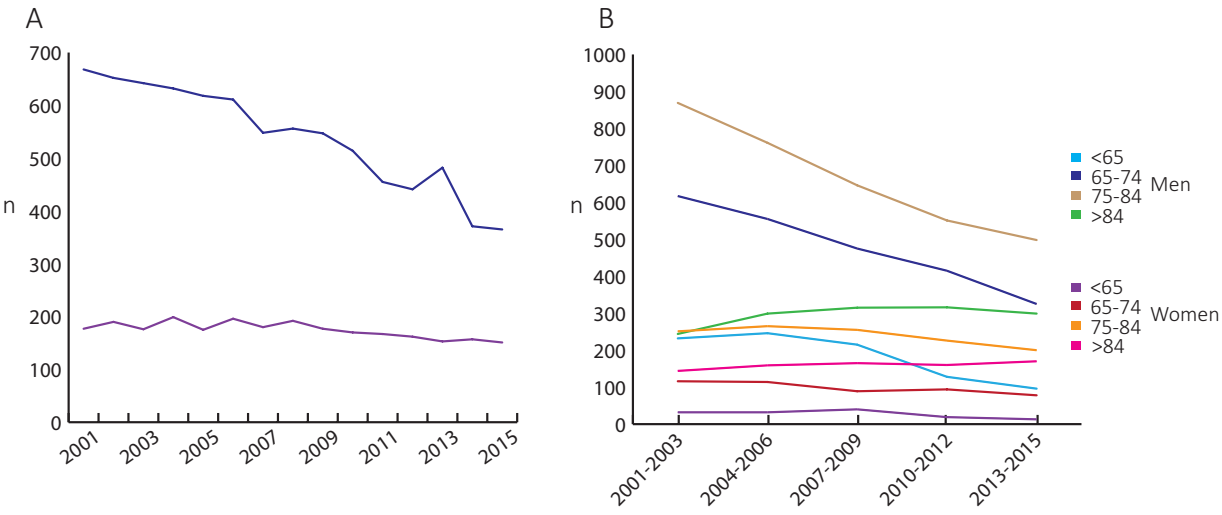

Figure XI. Time trends in sex differences for patients with ruptured abdominal aortic aneurysm (rAAA). **A.** Total number of ruptures per year, blue line represents men, purple line represents women. **B.** Total number of ruptures per year according to age group.

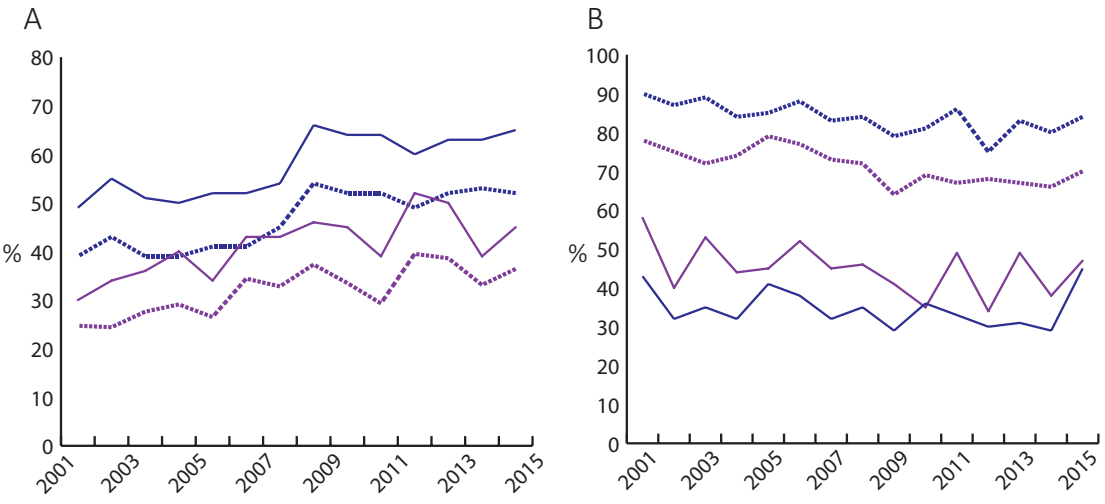

Figure XII. Time trends in sex differences for patients with ruptured abdominal aortic aneurysm (rAAA). Blue line represents male individuals, purple line represents female. **A.** Overall repair rates of all diagnosed patients with rAAA per year (dotted lines) and repair rates of all patients diagnosed in-hospital (connected lines). **B.** Postoperative 90-day mortality for treated rAAA (connected lines). Overall mortality for all individuals with rAAA (dotted lines).

Postoperative complication rates were similar for men (33.1 %) and women (35.1 %), p=0.210. The distribution of complications was equal in women and men. The three most common complications were: prolonged stay in the intensive care unit (ICU) >5 days, renal failure and multiple organ failure (MOF), *figure XII*.

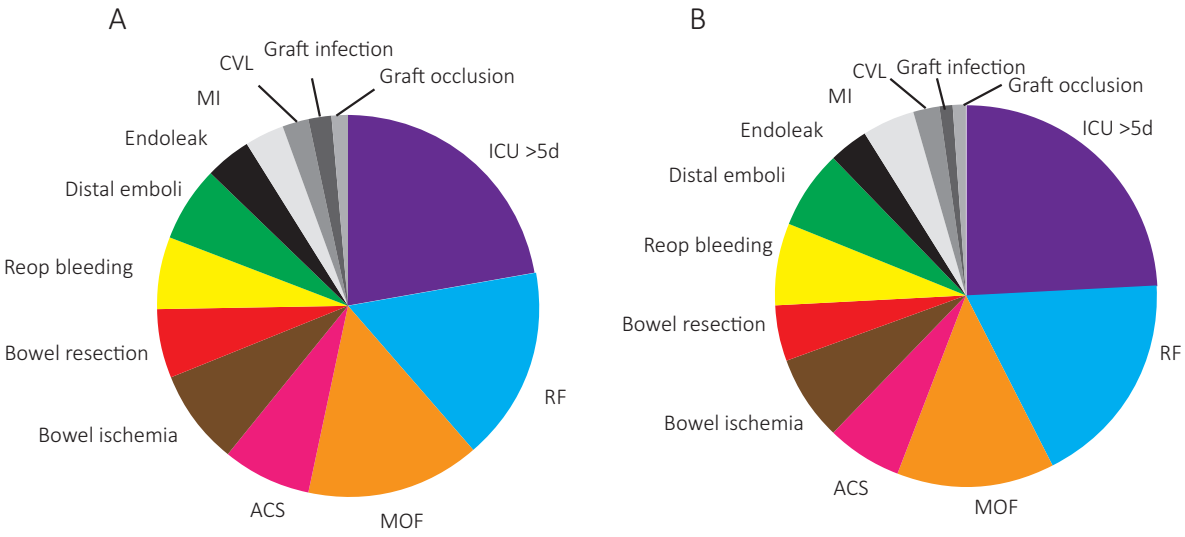

Figure XIII. Pie charts illustrating the distribution of complications in women (A) and men (B) after rAAA repair between 2009–2015.

Abbreviations: ICU >5d=stay in intensive care unit >5 days, RF=Renal failure, MOF=Multiple organ failure. ACS=Abdominal compartment syndrome, MI= Myocardial infarction, CVL=Cerebrovascular lesion.

5.2 DISCUSSION

5.2.1 Untreated rAAA

The rAAA demands early diagnostics and swift relay to the operating theatre or angio-suite. Left untreated or misdiagnosed, death is an almost certain entity. Even when treated, one in three suffer the same devastating result. For a long time, studies of AAA failed to include or report on the proportion untreated, a limitation also mentioned in a systematic review with meta-analysis of sex differences in morphological eligibility for EVAR.[180] Failing to do so can lead to misunderstandings regarding rAAA epidemiology and its outcome. In **Study I**, the reported low proportion of untreated contradicts the previous assumption of high untreated rates.[56, 70, 83] The higher proportion of untreated in a national setting from **Study IV** was partly

due to the inclusion of data from the CDR and hence differs from **Study I** where only individuals reaching an emergency department were included. However, when only including patients that were recorded in the NPR in **Study IV**, repair rates were 46 %, still lower than in our regional material. In the Stockholm county region where **Study I** was performed, an EVAR first strategy has been implemented during the last decade. From previously, where there was hesitation about transferring a patient with rAAA, more patients are now transported from their primary hospital to one of the two hospitals in the region with vascular expertise and resources. The benefits of this have been studied and reported on[70] and are in concordance with current recommendations[19]. Increased use of EVAR might also allow older and more unwell patients to be eligible for repair as it can be performed without general anesthesia or laparotomy.

5.2.2 Previously detected

The immediate threat to life and the high mortality for rAAA calls for a high level of resources and skill within the hospital walls.[70] However, early identification of patients with intact AAA in the population is the most effective tool to minimize the number of rAAA. Our second study (**Study II**) found that in one third of patients with rupture, the AAA was previously known. This is a high proportion and an aspect of the rAAA disease rarely studied or mentioned. Among the 85 patients (30 %) with a previously known AAA, an alarmingly high proportion (31 %) were missed in surveillance or never referred to a vascular surgeon. This is an area in which care-givers and health professionals must improve. Structured surveillance regimes must be developed, implemented and maintained. Furthermore, the awareness among health care providers regarding the necessity of referring AAA patients for evaluation at a vascular department must be enhanced.[19] It is also important to recognize that surveillance is not only for preoperative use, but after EVAR, life-long surveillance with repeated imaging is important to avoid secondary sac rupture.[181, 182] The influence of SEP, such as level of education, might be of importance in this aspect of previously detected AAA. Not fully understanding disease pathophysiology and risk assessments might impair patient compliance and prognosis, as further examined in **Study III**.

5.2.3 When to treat AAA

In **Study II** AAA-size as reason for non-repair comprised a small group (13 %) within the proportion of previously detected AAA among rAAA patients. Although rupture in patients with AAA diameter <55mm is rare, it can occur, and likewise, not all large AAA rupture. A systematic

review of 14 eligible studies concluded that rupture rates from small AAAs lie between 0 and 1.61 per 100 person-years.[183] However, heterogenicity among the studies and the absence of clear reporting standards for aneurysm rupture hindered the analysis. Suggestions that lower mortality after EVAR should prompt lower diameter threshold was discarded by a Cochrane analysis of four randomized trials.[184] The 55 mm threshold is somewhat arbitrary but partly based on autopsy reports on 24,000 consecutive individuals.[185] In that study, among those with AAA (473), 118 were ruptured. Approximately 40 % of AAAs >50 mm in diameter were ruptured. In the same study, 40 % of AAAs between 70 and 100 mm were not ruptured, whereas 13 % of AAAs <50 mm were ruptured. Perhaps the use of ASI[80, 81] and consideration of other patient characteristics such as sex[85, 170] and aneurysm morphology[186, 187] could help determine which patients to operate on and when. Nevertheless, long-term prospective studies of these factors are necessary before inclusion in risk assessment protocols.

5.2.4 Get rich or die trying

Study III represents the largest study of individualized SEP and its effect on presentation of disease (iAAA or rAAA) set in a welfare-state such as Sweden. The effect of spending capability versus that of level of education is partly separate and the results in Study III might reflect this; a healthy lifestyle is associated with income and reflects the individuals capability of acquiring healthy foods, exercise and travel, whilst understanding disease pathophysiology and understanding when to seek care is often attributed to educational level[157, 188]. In the case of Study III, education may play a more important role in understanding disease and symptomology as well as adherence to screening programs, while income may affect overall cardiovascular comorbidity. The association between low SEP and presenting with rAAA rather than iAAA was seen in a Dutch study of 1,178 patients.[164] The same results in Study III with 41,222 patients further strengthens this association. Low SEP also affects screening attendance.[30, 189] Study III and IV have indicated worse outcome for women and patients with low SEP. Even smoking, a main risk factor for AAA development and growth is associated with low SEP.[190] The association between low SEP and worse outcome of AAA disease is therefore present from AAA formation, through growth and detection, to presentation and repair outcome. Information on SEP can be used to reduce smoking prevalence by targeted programs, to increase screening attendance by offering free screening and to improve patient outcome by better patient information and individualized surveillance both pre- and postoperatively.

5.2.5 Sex differences

In both **Study I** and **Study IV** inequality between the sexes was examined at the regional and the national levels respectively. From **Study I**, the findings of similar repair rates and outcome were of great interest as they contradicted what, at that time, were sure assumptions of inequality in care between the sexes. What that study lacked however, was data on rAAA patients not admitted to a hospital and the results might only be applicable to a similar metropolitan area. The smaller population studied might also be grounds for type II errors. In **Study IV** sex differences in repair rates and short term outcome were clear. However, the lack of sex difference in long-term mortality seen in our sub group analysis could be a result of an overrepresentation of more comorbid male patients in the latter rupture cohort that has not adhered to screening programs. Some studies suggest similar results as **Study IV**.[71, 84-86] However there are contradicting reports[191] that could be explained by differences in study variables and outcome measures. For instance, in our study a high proportion were treated with EVAR which was not the case in some of the other studies with opposing results[71] and while **Study IV** presents both short and long-term data on postoperative mortality, others only present in-hospital data.[86] Sex differences have been shown to be prominent in studies of iAAA where women are more often not offered repair, are less eligible for EVAR and have higher postoperative mortality.[180] **Study IV**, one of the largest studies of sex differences in rAAA did not find women less eligible for EVAR but the difference in overall repair rates and postoperative mortality, especially 30-day mortality, was clear.

5.2.6 Outcome

Postoperative mortality rates after rAAA have improved, as shown in **Study III** and **IV**. The introduction of permissive hypotension and evidence-based blood transfusion regimes in rAAA patients[192-194] might have improved survival outcome. Structured protocols or algorithms for managing rAAA have been shown to decrease the relative risk of 30-day mortality by 35 %.[121] Overall mortality after rAAA does not seem, however, to be in decline and is concordant with a study from Denmark that found that when adjusting for age, no change in overall mortality from rAAA was seen between 1994–2008.[60] Similar results have been reported from Norway.[110] Both these studies are from Nordic countries with similar health care systems as in Sweden. However, contradicting reports claim a decrease in rAAA mortality.[25, 66, 67] These studies often lack the inclusion of out-of-hospital death and therefore may underestimate the overall mortality from rAAA.

5.3 METHODOLOGICAL CONSIDERATIONS

All studies included in this thesis are to be considered observational studies, meaning that the researcher does not manipulate the exposure or influence the distribution of the exposure among the subjects. This is unlike the experimental study where the exposure is imposed on subjects by the researcher. This latter form of study is what is usually seen as a randomized trial, designed in an effort to erase confounders or at least have them evenly distributed between the different groups studied. Although this method is to be preferred when possible, certain conditions such as a rare disease or ethical considerations hinder a randomized trial and an observational study may better suit the cause. When matching is performed, different characteristics are taken into consideration in order to make the study groups as similar as possible so as to better assess the exposure effect.

Study I and II. These studies only include those individuals who reached a hospital and were diagnosed with a rAAA either by clinical and/or radiological signs. We know that a proportion of rAAA patients die at home and with massively decreasing autopsy rates in Sweden for the elderly, the true incidence of rAAA will remain unknown. Subgroup analysis results in small number of patients being included, hence the results must be interpreted with caution. These studies represent the population of Stockholm and Gotland counties. A comparative study with the same outcomes from a more rural part of Sweden would have been interesting to perform.

Study III. Although the CDR was included for the search for individuals with AAA disease, it still contains the same limitations as described for Study I and II. One must also consider whether autopsy rates differ among the SEP strata, possibly affecting the outcomes of this study. This has, however, not been shown to be evident.[195] The study aimed to detect the initial diagnosis of AAA disease. To accomplish that, all registries were audited from 1995 onward but only those with an initial diagnosis of iAAA or rAAA between 2001–2015 were included. That left us with the assumption that the included individuals did not have a prior diagnosis before 1995. Level of disposable household income was extracted for the year prior to the initial diagnosis so as to reflect a full year's income and better correlate with the income quintiles. The lack of smoking as a comorbidity factor is regrettable but difficult to manipulate, but chronic obstructive pulmonary disorder (COPD) was used as a proxy instead.

Study IV. Today, the gold standard approach for estimating treatment effects is a RCT where the random allocation ensures that confounders, measured and unmeasured, will be evenly

distributed between the groups. A PS analysis tries to mimic this fundamental quality of a RCT by accounting for differences in baseline characteristics. The PS is a balancing score, meaning that conditional on the PS, the distribution of measured baseline covariates is similar between treated and untreated subjects. In this current study, matching individuals on their PS and then observing the outcome (i.e. repair, EVAR or mortality after repair) one can assume that the compared women and men (1:3 ratio) are similar in all aspects except sex. This is comparable to the terms of a randomized trial setting where the randomization itself creates an even distribution of predictors. Unlike a regression model where confounders are inserted into the model because they affect exposure and outcome, a PS model incorporates confounders in the probability of the exposure (i.e. female sex in this study) and only on the combined PS does the model then predict outcome. The PS model has its limitations in that it only controls for variables inserted as predictors. Any missing or non-detected variable of importance cannot enter the model.

5.3.1 External validity

External validity describes the generalizability of the results to a larger demographic than the studied individuals. With the proper study design, a higher external validity can be achieved. Using population-based material is one way of achieving a high external validity but is only generalizable for the studied population. I.e., the results of Study I and II are generalizable to the counties of Stockholm and Gotland or to a county similar to these. Study III and IV are nationwide population-based studies and the results are therefore generalizable to all inhabitants in Sweden and also to similar countries with comparable health care systems and ethnic composition.

5.3.2 Internal validity

Internal validity describes to what extent the study correctly measures what it was intended to measure. Different types of errors or biases can impair the internal validity of a study. These are described below.

5.3.3 Random error

A random error generally affects the precision of the study rather than affecting the results in any one direction. In order to understand how this is estimated it is necessary to understand the basics of hypothesis testing. For every research question the “null hypothesis” should be

defined, assuming that there is no correlation between the investigated exposure and outcome. Commonly used estimates of the level of random error include Confidence Interval (CI) and p-value. A 95 % CI states an interval within which the estimated result would fall 95 % of the time if the study was performed repeatedly under the same conditions. The p-value indicates the probability that the null hypothesis stands true despite the observed results. A Type-I error occurs when the null hypothesis is rejected despite being true. This can occur when multiple testing for significance is performed. A Type-II error occurs when the null hypothesis is accepted despite being false and is often due to insufficient power (small population) in the statistical analysis. The lack of sex differences in Study I may be due to a Type-II error as Study IV with a larger study population demonstrated opposing results. The loss of sex differences in the sub groups analysis performed in Study IV could be the result of a Type-II error as the included population was much smaller than the overall study group.

5.3.4 Bias

A selection process where selected subjects are not representative of the intended study population leads to *selection bias*. For this thesis, the rAAA diagnose comes with its inherent selection bias as an unknown proportion of rAAA patients die at home or in a hospital without autopsy or proper diagnosis. Although Study III and IV included data from the CDR, low autopsy rates cause possible selection bias, as does the inclusion of those patients only reaching an emergency department (Study I and II). Another form of bias, information bias or misclassification, occurs when different variables including exposure and outcome are registered or classified differently amongst subgroups in the study leading to an inherent skewness and error in comparing different groups. The Swedish NPR is validated with extremely good coverage of inpatient data.[176]

5.3.5 Confounder

A variable that is associated with both the exposure and the measured outcome is called a confounder. In a randomized trial the confounders are assumed to be evenly distributed so as not to cause any interference with the results. In observational studies, however, confounders must be identified so that they can be adjusted for in the model or to help stratify the study groups. For AAA disease, age is a typical confounder affecting both the development of the disease (exposure) and postoperative mortality (outcome). Both Study III and IV incorporate and adjust for this in their statistical models.

6 CONCLUSIONS

Apparent positive trends in the care of men with rAAA can be found that could be partly associated with the implementation of screening, and possibly improved cardiovascular prevention in the population. However, the results unfortunately do not reflect equally in the female population. Alarmingly, our results emphasize the presence of inequality in the health care system for women and those with low income and low level of education.

Study I. Our results and other contemporary studies show a shift toward a higher rate of treated patients with rAAA, and improving outcomes, similar for women and men. The increased use of EVAR contributes to this improvement in short-term outcome. High age influences the willingness to treat patients with rAAA.

Study II. One-third of patients admitted with a rAAA had a previously detected AAA. The surgeon's decision to deny elective surgery and surveillance deficiency were the two main reasons for non-repair at time of the AAA diagnosis. Improved patient-specific protocols to reduce the surveillance gaps and new methods of determining rupture risk in each case of AAA could be two possible future strategies to reduce the incidence of rupture.

Study III. The incidence of rAAA is decreasing. Individuals with low SEP have a higher risk of presenting with rAAA rather than iAAA. They also fare worse after repair. Consequently, SEP should be regarded as a relevant risk factor that should be included in considerations for improved care flow of patients with AAA.

Study IV. Female sex is associated with lower repair rates and higher mortality after repair for rAAA, the latter was most evident for 30-day mortality. No difference was observed in the association between sex and repair type.

7 FUTURE PERSPECTIVES

Studies on targeted screening invitations to individuals with low SEP as well as possible changes to patient fees should be performed to determine if screening attendance improves.

Further studies of subgroups of small AAA among women should be initiated to better clarify if threshold diameter for intervention for women should be lowered to avoid rupture in this group. A large RCT that is not underpowered would be ideal, including subgroups of smoking and non-smoking women.

SWEDVASC has improved its coverage yearly and is now a good platform to use for further research into AAA disease and vascular surgery in general. The collection of data on smoking habits is a useful variable in the registry that could be used in future studies.

Studies on the association between SEP and iAAA are a natural next step to see if differences are also evident in the patient with an iAAA. So is studying the proportion of previously detected AAA in rAAA patients on a nationwide basis, as well as observing differences in those rates over time.

The findings in Study III and IV also have implications beyond AAA and vascular surgery.

Sex differences are evident not only in AAA disease but many other areas of interest such as malignant melanoma. Using Swedish register data and data from the Swedish cancer registry, this area can be further explored.

Differences in SEP have implications in other fields of surgery such as breast cancer, breast cancer reconstruction and other malignancies. It would be advisable to study this further in those clinical settings.

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Jag har fötterna i poolen
Inte fötterna på jorden
Huvudet bland molnen
Om inte huvudet är på månen

– Sakarias