LIFESTYLE AND RISK OF ABDOMINAL AORTIC ANEURYSM

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Stockholm 2016

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background

Lifestyle-related factors associated with abdominal aortic aneurysm (AAA) disease are very scarcely investigated in prospective design. Identification of such could provide better understanding of AAA epidemiology and etiology, and provide new hypotheses for studies on AAA growth rate in order to try to limit progression of the disease. The overall aim of this thesis was to study possible associations between modifiable, lifestyle-related factors and risk of AAA.

Methods and Results

Two prospective population-based cohorts of 84,890 middle-aged and elderly men, and women, from Central Sweden (the Cohort of Swedish Men and the Swedish Mammography Cohort) constituted the study population for all studies in this thesis. In Study I-IV, AAA diagnosis and/or repair was identified over the 12- to 14-year follow-up in the Swedish National Patient Register, the Swedish Cause of Death Register, and the National Register for Vascular Surgery (Swedvasc). In Study V, abdominal aortic diameter (AAD) was assessed in 14,249 men screened for AAA (AAD ≥30 mm) between 65 and 75 years of age (mean 13 years after baseline, 1 January 1998). Linear regression models were used to estimate mean AAD, and Cox proportional hazards regression models were used to estimate hazard ratios (HR) of AAA as a measure of AAA risk, by comorbidities and self-reported lifestyle-related exposures, with corresponding 95% confidence intervals (CI's).

We observed that smoking was associated with an increased risk of AAA, and with an increased mean AAD among men. Across all specific smoking strata, the absolute risks of AAA were higher among men, while the relative risks seemed to be more pronounced among women. The AAA incidence was higher among smoking women than among never smoking men. Following smoking cessation, women had a more rapid decline in excess risk associated with current smoking than men did. Furthermore, obesity seemed to be associated with an increased AAA risk; central obesity (i.e. increased waist circumference) was associated with AAA diagnosis and/or repair, while total obesity (i.e. increased BMI) was associated with screening detected AAA, and with a larger mean AAD, among men.

We also observed that consumption of fruits, but not vegetables, was associated with a decreased risk of AAA, an association that seemed to be more pronounced with ruptured AAA than with intact AAA. No association was observed between a healthy diet in general and risk of AAA detected at screening among men. A moderate consumption of total alcohol (i.e. ethanol) was associated with a lower risk of AAA diagnosis and/or repair, but not among participants free from cardiovascular disease (CVD). Alcohol consumption was also associated with a smaller mean AAD among men. The most commonly consumed alcoholic beverages – beer among men and wine among women – were inversely associated with AAA diagnosis and/or repair, whereas no association was observed for spirits.

Last, when compared with those who almost never walked/bicycled, men who were walking/bicycling >40 min/day had a lower risk of having an AAA at screening. Among men, CVD was associated with a larger predicted mean AAD, and with an increased risk of AAA detected at screening.

Conclusions

Lifestyle-related exposures were prospectively associated with AAA disease, and with mean AAD. Regarding risk of AAA, current smoking may affect women to a greater extent than men, obesity may increase the risk, and consumption of fruits, a moderate consumption of alcohol, and physical activity, may reduce the risk.

LIST OF PUBLICATIONS

I. **Stackelberg O**, Björck M, Larsson SC, Orsini N, Wolk A.
    Sex differences in the association between smoking and abdominal aortic aneurysm.
    British Journal of Surgery. 2014;101:1230-1237.

II. **Stackelberg O**, Björck M, Sadr-Azodi O, Larsson SC, Orsini N, Wolk A.
    Obesity and abdominal aortic aneurysm.
    British Journal of Surgery. 2013;100:360-366.

III. **Stackelberg O**, Björck M, Larsson SC, Orsini N, Wolk A.
    Fruit and vegetable consumption with risk of abdominal aortic aneurysm.
    Circulation. 2013;128:795-802.

IV. **Stackelberg O**, Björck M, Larsson SC, Orsini N, Wolk A.
    Alcohol consumption, specific alcoholic beverages, and abdominal aortic aneurysm.
    Circulation. 2014;130:646-652.

V. **Stackelberg O**, Wolk A, Eliasson K, Hellberg A, Bersztel A, Larsson SC, Orsini N,
    Wanhainen A, Björck M.
    Lifestyle and risk of screening-detected abdominal aortic aneurysm in men –
    A prospective population based cohort study.
    [Submitted]

The articles will be referred to in the text by their Roman numerals, and are reproduced in full at the end of the text.

RELATED PUBLICATIONS

- Harris H, Håkansson N, Olofsson C, **Stackelberg O**, Julin B, Åkesson A, Wolk A.
  The Swedish mammography cohort and the cohort of Swedish men: study design and characteristics of two population-based longitudinal cohorts.
  Open Access Epidemiology. 2013;1:16.

- **Stackelberg O**, Delle M, Berger M, Wanhainen A, Mani K, Lindström D, Lundberg G, Gillgren P.
  Visceral stent patency after endovascular treatment of aortic diseases.
  [Manuscript]

LIST OF ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
AAD	Abdominal Aortic Diameter
BMI	Body Mass Index
CDR	The Cause of Death Register
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
EVAR	Endovascular Aneurysm Repair
FFQ	Food Frequency Questionnaire
HDL	High Density Lipoprotein
HR	Hazard Ratio
iAAA	Intact Abdominal Aortic Aneurysm
LDL	Low Density Lipoprotein
LELE	Leading Edge to Leading Edge
MAR	Missing at Random
MCAR	Missing Completely at Random
MICE	Multiple Imputation by Chained Equations
MNAR	Missing Not at Random
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NDR	The National Diabetes Register
NPR	The National Patient Register
OTO	Outer to Outer
rAAA	Ruptured Abdominal Aortic Aneurysm
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SD	Standard Deviation
Swedvasc	The Swedish National Register for Vascular Surgery
WHO	World Health Organization

CONTENTS

BACKGROUND

Introduction

The term aneurysm derives from the Greek word *ανεύρυσμα*, which means widening. In medical terminology, an aneurysm refers to a permanent and local widening, or dilatation, of a blood vessel which can emerge in any vessel of the body. An arterial aneurysm refers to a dilated artery, while an abdominal aortic aneurysm (AAA) refers to a dilatation of the abdominal part of the aorta. Such dilatation is a result of a weakened aortic wall and, when situated in the abdomen, is most often observed below the renal arteries (Figure 1).

The dilatation in AAA disease is a slow and gradually expanding process, which could expand to a point when the aortic wall is too weak to contain the pressure of the blood flowing through the aorta, resulting in a rupture of the wall. Such catastrophic event is associated with high mortality rates due to a major blood loss in to the abdominal cavity. The principle of treatment of an AAA is to exclude the aneurysm from circulation by replacing the dilated part with a synthetic graft, achieved either through open surgery, or through an endovascular operation. Preferably, repair is to be performed prior to rupture in order to decrease the risks associated with such event, but repair can also be performed if rupture already has occurred since death otherwise is virtually inevitable. In order to detect AAAs before rupture occurs, screening programs for AAA with abdominal ultrasound are being widely implemented. Much of the etiology of the disease is unknown and to date, there is no medical strategy except for smoking cessation to decrease growth and rupture rate of small screening-detected AAAs. Identification of modifiable lifestyle-related factors associated with risk of developing AAA may, therefore, contribute to find means of decreasing rate of growth, rupture, and the need for AAA repair.
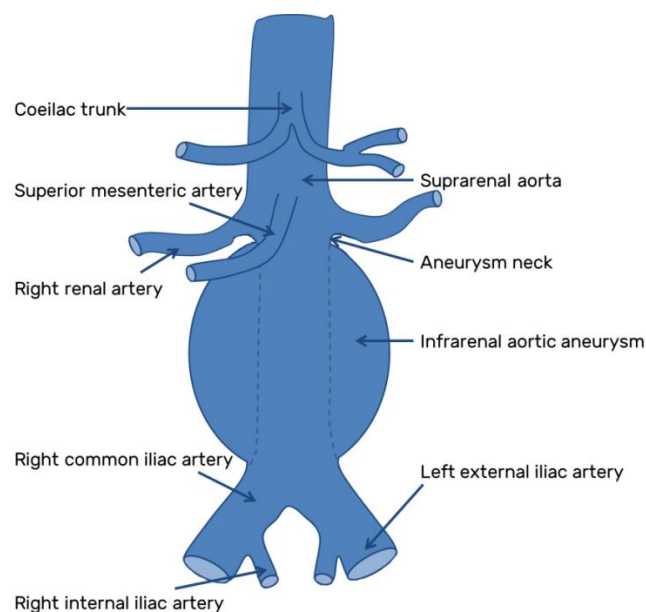

Figure 1. Schematic drawing of an infrarenal abdominal aortic aneurysm. Dashed lines represent the contour of a non-aneurysmatic aortic wall.

Historical notes

Problems and complications because of an aneurysm has been recognized for nearly 4000 years (Osler, 1905). In the 2nd century AD, Marcus Antonius Antyllus was the first to give a description of causes and treatment of an aneurysm per se. In 1555, Andreas Vesalius (1514-1564), the Belgian anatomist and physician described as the father of modern anatomy, was one of the first to clinically describe an AAA (Fortner et al, 1984). First carried out in 1785, John Hunter (1728 - 1793) introduced remote proximal ligation of a popliteal aneurysm, a method that relied on the development of collateral vessels to circulate the distal limb. Three of the five operations he had time to perform were deemed successful, and one of the patients survived for over 50 years (Galland, 2007). Sir Astley Cooper (1768-1841) was, in 1817, first to attempt to treat an AAA by ligation of the infrarenal aorta (Cooper, 1830), a principle of treatment primarily chosen to treat aneurysms during the 18th and 19th century. Ligation of the aorta could, however, lead to visceral and peripheral ischemia, which is why many different and unsuccessful techniques were introduced during the late 19th and early 20th centuries (e.g. external compression, wiring and electrocoagulation, as well as cellophane wrapping, the treatment offered to Albert Einstein).

After the Second World War, heparin was introduced and surgeons began to recognize the importance of blood replacement, and realize the value of antibiotics. Subsequently, the advancements led to Norman E. Freeman and Frank H. Leeds succeeding with the first AAA repair in 1951 (Freeman et al, 1951). Two years later, Henry Bahnson succeeded with repair of a ruptured AAA (Bahnson, 1953). At first, homologous transplants were used as aortic replacement, a strategy that later was replaced by the use of synthetic graft prostheses with better durability (e.g. Vinyon-N cloth (Voorhees et al, 1952) and knitted Dacron (De Bakey et al, 1958)). Combined with the inlay technique, aortic replacement with grafts of knitted Dacron, or expanded polytetrafluoroethylene (Gore-Tex®), still remain the number one choice for open AAA repair (Zarins et al, 1997).

In 1985, the Ukrainian surgeon Nicholai L. Volodos was first to perform surgery using an endovascular approach (Diethrich, 2013; Volodos, 2015). The 66-year-old patient had a stenotic iliac artery, and occluded superficial femoral and popliteal arteries, that had resulted in gangrene of the lower limb. Dr. Volodos managed the condition with an operation that today would be referred to as a hybrid operation; deployment of an endovascular stent in the iliac artery, followed by a femoro-tibial bypass. Even though Dr Volodos' team presented their research at various meetings in the Soviet Union, and published a report in Russian language in 1986 (Volodos et al, 1986), and one in English in 1991 (Volodos et al, 1991), their progresses failed to reach the West due to the isolation of the Iron Curtain.

It would take until 1991, when Juan Carlos Parodi published a report in English, before the method was widely introduced across the globe (Parodi et al, 1991). By that time, Dr Volodos' team had already managed to perform 18 stent-graft procedures of the iliac arteries, one successful treatment of a false aneurysm in the thoracic aorta, attempted to treat an AAA, and started to treat complex pathologies of the aortic arch (Volodos, 2015).

After a series of disappointing long-term results following the first generation of stent grafts (Guidoin et al, 2000; Holzenbein et al, 2001), technical advancements have eventually led to lower perioperative mortality, and virtually similar mortality on long term, as those associated with open repair (Stather et al, 2013). However, cautious considerations of advantages and disadvantages with both techniques still need to be made when deciding method of treatment, and whether the condition should be treated at all (Moll et al, 2011).

"I want to go when I want. It is tasteless to prolong life artificially. I have done my share, it is time to go. I want to do it elegantly" – Albert Einstein when his AAA, previously treated with cellophane wrapping, ruptured in 1954 (Cohen et al, 1990).

Pathophysiology

The abdominal aortic wall consists of three layers, all of which provide different functions for the aorta; the tunica intima, media, and adventitia (Humphrey et al, 2012) (Figure 2). The thin intima is the innermost layer, made up of endothelial cells and reinforced with helically arranged fibres underneath that provide a smooth surface for blood to flow across. The media, the middle layer, consists of proteoglycans and approximately 30 elastic lamellae of organized collagen alternating with abundant circulatory oriented smooth muscle cells. This configuration allows the aorta to absorb and contract the tensile stress following each heartbeat. The most outer layer is the adventitia, which mainly is composed of collagen supported by an external elastic lamina which provides additional support and structure to the aorta. The partly reversed flow (leading to an oscillatory wall shear stress) observed in hemodynamic studies (Amirbekian et al, 2009), and the relatively low number of elastic lamellae (Wolinsky et al, 1969), have been suggested as an explanation to why the infrarenal aorta is most susceptible for aneurysm formation.

The exact mechanisms that initiate and stimulate the progression of an AAA are, however, to a large extent unknown. The disease was previously considered a manifestation of systemic atherosclerosis, but later evidence rather suggests the two to be co-existing factors that may or may not contribute to the development of the other (Golledge et al, 2010; Johnsen et al, 2010).
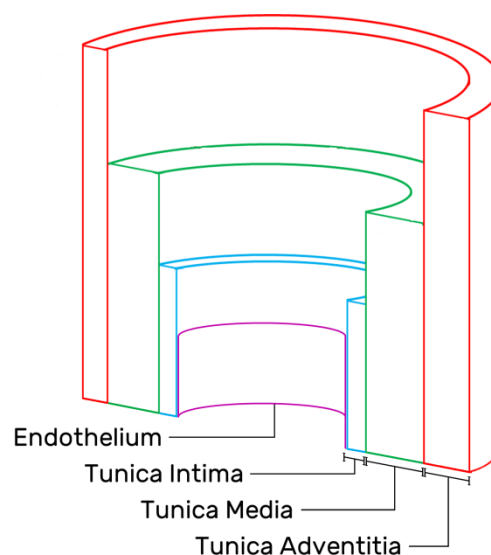

Figure 2. Schematic drawing of the three layers (tunica) of the aortic wall. The endothelium is part of the intimal layer.

Most of the pathophysiological evidence to date derives from cross-sectional studies on humans (e.g. aortic tissue histology, or circulating biomarkers), and from animal models. Recognized from these studies is that the aortic wall of an AAA exhibits a chronic and transmural inflammation, a degradation of connective tissue proteins within the tunica media and adventitia (Brophy et al, 1991; Pearce et al, 1996; Shah, 1997), and smooth muscle cell apoptosis in the media (Boddy et al, 2008). During aneurysmal formation, there is a loss of medial and adventitial elastin (Campa et al, 1987; Dobrin et al, 1984; White et al, 1993). Given the constant tensile stress by the arterial blood pressure, hemodynamic forces also contribute to aneurysmal degeneration, as to the risk of rupture (De Keulenaer et al, 1998). During the later stages of disease, prior to or at the event of rupture, there is an additional degradation of adventitial collagen that exceeds the production of the same (Thompson et al, 1999). A gradual imbalance between factors weakening the aortic wall, and a compensatory response acting to resist tensile wall stress, might be a simple pathophysiological explanation through which the aneurysm disease operates (Thompson et al, 1999).

Of the factors associated with AAA prevalence (described more in detail in later chapters), only diabetes mellitus and smoking has been consistently associated with AAA growth rate (Sweeting et al, 2012). Therefore, it has been suggested that different factors may affect AAA initiation as opposed to progression (Golledge et al, 2006). Other key processes identified and characterized in studies on AAA pathophysiology include autoimmune reactions, oxidative stress, thrombosis, and production of a vast amount of circulating signaling molecules, such as interferon-gamma (Abdul-Hussien et al, 2010; Boddy et al, 2008; Dua et al, 2010; Golledge et al, 2009; Kuivaniemi et al, 2012; Shimizu et al, 2006).

Epidemiology

Epidemiology is the core of public health science and has been simplistically defined as *"the study of the distribution and determinants of disease frequency"* (MacMahon et al, 1970).

Descriptive statistics

The best available data on AAA prevalence is provided from contemporary population-based screening studies (Moll et al, 2011). Autopsy studies have also provided valuable historical data (Bengtsson et al, 1992).

During the 1980's to the early 2000's, the prevalence of AAA among elderly men was reported around 4% to 9% (Ashton et al, 2002; Lederle et al, 2000; Lindholt et al, 2005; McCarthy et al, 2003; Simoni et al, 1995; Wilmink et al, 1999b). Some studies also reported trends that the prevalence of AAA was increasing between the 1950's and the 1990's (Acosta et al, 2006; Filipovic et al, 2005; Lilienfeld et al, 1987; Melton et al, 1984). However, more recent reports rather indicate the opposite, with a reported prevalence among 65-year-old men ranging from 1.1% to 2.6% in Western countries during the last years (Anjum et al, 2012; Choke et al, 2012; Darwood et al, 2012; Grondal et al, 2015; Svensjo et al, 2011). Such decline, however, has not been observed globally, most likely explained by international differences in distribution of common cardiovascular risk factors (in particular smoking) (Sidloff et al, 2014).

Due to the low prevalence and the long, and usually asymptomatic, course of AAA development, true incidence of the disease is hard to estimate without continuous ultrasound measurements over a long time period in a large population. One of the only prospective studies with ultrasound measurements at baseline and at end of follow-up investigating factors associated with AAA incidence is the Tromsø Study (Forsdahl et al, 2009). In that study, a cohort of 2035 men and 2310 women, aged 25 to 82 years, were followed-up between 1994 and 2001. The mean annual incidence of AAA was 0.4% (Forsdahl et al, 2009). As for Sweden, some studies have estimated rates of incident AAA diagnosis, repair, and rupture (Hultgren et al, 2012; Mani et al, 2013).

Between 1990 and 2005, results from a Swedish register-based study indicated that the incidence of AAA diagnosis varied over different regions in Sweden. Among men, the highest standardized incidence rate was observed in the northern parts; 102.7 cases per 100.000 person-years. In the mid- and south of Sweden, respectively, the rate was 86.5, and 74.4. Corresponding numbers among women were 30.6, 26.8, respectively 21.9 cases per 100.000 person-years (Hultgren et al, 2012). In another Swedish register-based study of people aged 50 years or older, intact AAA repair was found to have increased between 1994 and 2010; the rate per 100,000 person-years was 18.4 between 1994 and 1999, 19.4 between 2000 and 2005, and 24.0 between 2006 and 2010. In that study, ruptured AAA (rAAA) repairs decreased after 2005; the rate per 100.000 person-years was 9.3 in 1994 to 1999, 9.3 in 2000 to 2005, and 8.4 in 2006 to 2010 (Mani et al, 2013).

Risk factors

Risk factors are factors that have been observed to be associated with risk of a certain disease. They can either be modifiable (e.g. lifestyle), or non-modifiable (e.g. age and sex). Apart from enabling primary prevention of the disease by modifying factors affecting the risk of disease development, identification of such can also assist in better understanding of its pathophysiology.

Age

The abdominal aortic diameter (AAD) is known to increase with age, as is the prevalence of AAA. In a study of 146 participants aged 4 to 74 years, age showed a very strong correlation with AAD in both men (r=0.92, p<0.001) and women (r=0.94, p<0.001), and the AAD between 25 and 70 years of age increased by 26% in men, and by 24% in women (Sonesson et al, 1994). In a study of 69,905 participants without AAA, aged 50 to 79 years, age was significantly associated with AAD. However, the effect was small in this age-group; 29 years increment in age was associated with a 1 mm increment in AAD (Lederle et al, 1997b). In another study of 10,061 men aged 60 to 75 years, the prevalence of large AAAs (≥40 mm) rose from 0.5% at age 60, to 5.7% at age 75 (Grimshaw et al, 1997). The median AAD (21 mm) did not, however, seem to differ over age groups, and authors estimated that age was associated with AAD in 25% of the population, indicating that age may only be associated with aortic dilatation in some specific groups of the population.

Sex

In several imaging studies of the AAD, women have been found to have an approximately 1 mm to 3 mm smaller AAD compared with men (da Silva et al, 1999; Lederle et al, 1997b; Sonesson et al, 1994; Wanhainen et al, 2008c). AAA is, however, much less common among women than among men, and the reported prevalence among elderly women ranges between 0.3% and 1.5% in the last decade (Forsdahl et al, 2009; Hupp et al, 2007; Ogata et al, 2006; Palombo et al, 2010; Savji et al, 2013; Svensjo et al, 2013). Despite this, women have a 3- to 4-fold increased risk of rupture when under AAA surveillance (Sweeting et al, 2012; UKSAT, 1998b), the average AAD at rupture is smaller (Laine et al, 2016; UKSAT, 1998a), and the outcomes after surgery tend to be worse (Giles et al, 2009; Hultgren et al, 2007), compared with men.

The inter-sexual differences in AAA disease have been speculated to be partly mediated by protective effects of estrogen, and partly by adverse effects of male androgens. The estrogen is believed to be protective through immunomodulation by reducing matrix proteolysis (Wu et al, 2009), and affecting processes thought to be of importance in AAA development (e.g. chronic inflammation, immune cell migration, cytokine production, and growth factor expression) (Sinha et al, 2006). In studies of rats, it has been observed that male rats with a transplanted female rat aorta develop AAA to the same extent as non-transplanted male rats (Ailawadi et al, 2004).

Furthermore, higher AAA growth rates among female rats that have undergone oophorectomy, and lower growth rates among rats injected with estradiol, have been observed (Wu et al, 2009). In another study, orchidectomy in male mice was observed to reduce the rate of AAAs to the same rate as female mice, and administered dihydrotestosterone increased the incidence in both male and female mice, while also resulting in a higher incidence of ruptures (Henriques et al, 2004).

Heritability

Already in 1977, it was suggested that there might be a hereditary component in AAA development when Clifton et al published a case series of three brothers, the only siblings of one family, that all underwent AAA repair (Clifton, 1977). In 1985, Norrgård et al observed that 12 out of 51 AAA patients had a first-degree relative with an AAA as well (24%), and that six patients (12%) had a second degree relative with the disease (Norrgard et al, 1985). Of the siblings to patients treated for AAA in Stockholm, Sweden, between 2008 and 2010, 11% were found to have an AAA as well (17% of the brothers, respectively 6% of sisters) (Linne et al, 2012). In a Swedish twin study, the risk of harboring an AAA was increased 71-fold if the monozygotic twin had an AAA, compared with if the sibling did not. Furthermore, the prevalence of AAA among participants with a monozygotic twin who had an AAA was 24% (Wahlgren et al, 2010). Apart from the higher prevalence, those with AAA heredity may be over-represented among those with large AAAs (Wanhainen et al, 2005), and patients with such heredity also seem to be younger (Darling et al, 1989). The pattern of inheritance have been suggested to be both X-linked and autosomal dominant (Darling et al, 1989; Tilson et al, 1984). Monogenetic studies, however, have failed to demonstrate strong associations between a specific gene and AAA disease (genetics of AAA reviewed in (Golledge et al, 2013)). Thus, it is likely that several genes interact with each other, or with environmental factors, and predispose for AAA development (Bjorck et al, 2013).

For example, a screening-study from Northern Sweden reported that atherosclerosis, smoking, and having a first-degree relative with AAA were all independently associated with AAA prevalence, but a combination of the factors seemed to interact multiplicatively on AAA risk (Wanhainen et al, 2005). Furthermore, polymorphisms on chromosome 9p21 have been shown to be associated with AAA (Bown et al, 2008; Helgadottir et al, 2008; Thompson et al, 2009), and an interaction between fruit and the chromosome demonstrates that a diet high in fruit may reduce the risk of myocardial infarction in individuals with that gene (Do et al, 2011). Thus, a possible effect of fruits and vegetables on AAA risk may be influenced by a gene-environment interaction.

Smoking

The association between smoking and AAA disease is well-known and was first described by Hammond and Horn in 1958 (Hammond et al, 1958). Authors reported, a decade later, that smoking seemed to be associated with AAA to an even larger extent than with other cardiovascular diseases (Hammond et al, 1969), findings that also have been confirmed more recently (Lederle et al, 2003). Being an active smoker seems to oppose the greatest risk; current smoking have been associated with a higher AAA prevalence (Lederle et al, 2000; Svensjo et al, 2011), aneurysm growth rate (UKSAT, 2002), and risk of rupture (Sweeting et al, 2012). Furthermore, when counting the etiological fraction, approximately 70% of detected AAAs have been attributed to smoking (Lederle et al, 2000; Svensjo et al, 2011). Also, one of few non-surgical strategies to decrease the risk of AAA expansion and rupture is smoking cessation (Baxter et al, 2008; Brown et al, 1999; MacSweeney et al, 1994). In Western Europe and North America, there seem to be a decline in AAA prevalence during the past years, indeed preceded by a decreasing frequency of active smoking among men (Svensjo et al, 2011).

Regarding risk of AAA, women seem to be more sensitive to smoking than men. For example, 18 out of 19 AAAs in a population-based screening cohort of 70-year-old women were detected either in current or former smokers, and the odds ratio for AAA disease was more than 20-fold increased among ever smokers, compared with never smokers (Svensjo et al, 2013). Women with large AAAs have shorter lifetime duration of endogenous hormone production, reflected by an earlier onset of menopause (Villard et al, 2011). In postmenopausal women, smoking has been associated with higher circulating levels of androgens (Brand et al, 2011; Sowers et al, 2010). Levels were, however, similar to that of a non-smoker after 1-2 years of cessation.

Smoking have not only been observed to affect the synthesis of collagen, oxidative stress, and alter the expression of metalloproteinases, but also to reduce estrogenic effects (Baron et al, 1990), and ovarian function (Sowers et al, 2010). Smoking women also experience menopause on average 1 year earlier than non-smokers (Sun et al, 2012). An altered balance between sex-hormones, and regulation of hormone receptors in the aortic wall, may explain an increased vulnerability of AAA among smoking women in relation to smoking men.

Obesity

Evidence for a possible association between obesity and AAA are inconclusive. It has been suggested that a release of pro-inflammatory adipokines and cytokines from peri-vascular adipose tissue may have an influence on AAA development (Barandier et al, 2005; Chatterjee et al, 2009; Eringa et al, 2007). A possible pathophysiological relation between obesity and AAA is, however, complicated by the somewhat contra intuitive fact that diabetes has been reported inversely associated with AAA prevalence in most studies (Lederle, 2012).

In a recently published meta-analysis, no differences in mean BMI between AAA patients and controls, or any association between BMI and AAA incidence, was observed (Takagi et al, 2015). Although much less studied, BMI was neither associated with growth rate of small AAAs in a meta-analysis that included five studies (3439 AAA patients) on the matter (Sweeting et al, 2012). BMI was neither associated with AAA expansion rate in the Veterans Affair study, where 567 AAA-patients were followed-up over a mean time of 3.7 years (Bhak et al, 2015). However, no study has used a meta-analytical approach to assess whether central obesity, as measured with waist circumference or waist-to-hip-ratio, is associated with AAA prevalence or growth rate. In a systematic review from 2013 (Cronin et al, 2013), three out of five studies that investigated BMI reported a positive association with AAA prevalence (Allison et al, 2008; Kent et al, 2010; Long et al, 2010), while two out of three studies that investigated waist circumference, or waist to hip ratio, reported significant positive associations with prevalence of the disease (Golledge et al, 2007; Lederle et al, 2000). Of the five studies, only Lederle et al accounted for both BMI and waist measures in their multivariable models, however, and authors reported a positive association between waist circumference and larger AAAs (≥40mm) (Lederle et al, 2000). Rather than total obesity, visceral abdominal fat have been observed to affect inflammation and formation of experimental AAA animal models (Police et al, 2009). Thus, a predominant localization abdominal fat, as among central obese people, may be of more importance in AAA disease.

Physical activity

It has been observed that physical activity is associated with a 20% to 30% lower risk of coronary heart disease (Sattelmair et al, 2011; Tanasescu et al, 2002). Furthermore, independent of the level of leisure-time physical activity, sedentary behaviors seem to be associated with an increased risk of cardiovascular diseases (Chomistek et al, 2013). The beneficial net-effects of physical activity and the adverse effects of sedentary behaviors on cardiovascular disease involves a direct action on the heart, altered levels of high-density and low-density lipoproteins (HDL and LDL), and effects on blood pressure, blood coagulability, and insulin sensitivity (Manson, 1996), which also may affect the risk of AAA development. A pure mechanistic effect due to adverse/pro-inflammatory haemodynamics in the abdominal aorta might also be altered through physical exercise, and may, thus, have an impact on the progression of the disease.

In a study of 10 AAA patients (Suh et al, 2011), mild levels of physical activity were correlated with an increase in mean wall shear stress (i.e. the frictional force induced by blood flowing across the inner wall surface), a decrease of oscillatory shear index (i.e. the extent of the fluctuations in wall shear stress over the cardiac cycle), and a decrease in particle residence time (i.e. how long blood particles stay in the aneurysm). Hence, mild exercise might be sufficient to reduce stagnant and oscillatory conditions in the abdominal aorta and thereby reduce AAA growth.

However, associations between physical activity, and inactivity, and AAA risk are very scarcely investigated in epidemiological studies. In the Life-Line Screening registry, data was reported from 3.1 million AAA-screened individuals at >20,000 screening sites in the United States, and authors observed a 14% decreased risk of AAA among participants who exercised ≥1 times per week, compared with those who exercised less than that (Kent et al, 2010). Furthermore, results from the Malmö preventive study indicated that physically inactive participants (e.g. those who did not walk or bicycle to work) had an increased risk of developing AAA (Lindblad et al, 2005).

Diet

Whether the diet affect AAA-development is debated. It has been reported that inhabitants in Mediterranean countries have a lower risk of coronary heart disease (Gjonca et al, 1997; Law et al, 1999; Richard, 1987; Rodriguez Artalejo et al, 1996; Tunstall-Pedoe et al, 1999), an association partly attributed to the Mediterranean dietary consumption pattern. However, in a screening cohort of 12,203 men from Western Australia, authors investigated a proxy for such diet, and no significant associations with AAA was observed in a multivariable model (Jamrozik et al, 2001). Authors concluded that an inverse association with a Mediterranean diet, if it at all exists, is more modest for AAA disease than for coronary heart disease (Jamrozik et al, 2001). In the Life-Line Screening registry, authors reported a 9% decrease in odds of AAA among individuals consuming fruits and vegetables, respectively a 10% decrease among those consuming nuts, >3 times/wk. Furthermore, consumption of meats and fast food was associated with a higher AAA prevalence in univariate analyses (Kent et al, 2010).

There are several potential pathways through which diet may affect AAA disease, of which a reduction in oxidative stress might be one (Miller et al, 2002). The inflamed aortic wall in AAAs is characterized by an increase in oxidative stress and might induce AAA formation through apoptosis of smooth muscle cells, proteolysis of matrix proteins, recruitment of cytokines and other pro-inflammatory cells, and through increased mechanical forces due to hypertension (McCormick et al, 2007a). Intake of antioxidants that have the potential to balance such stress could, therefore, potentially limit aortic wall inflammation and reduce the risk of AAA development.

Alteration of HDL and LDL levels is another potential effect of diet. Indeed, it was observed that a history of elevated LDL-, and of reduced HDL-, levels were associated with AAA development in a screening study from northern Sweden (Wanhainen et al, 2001). There are no available studies to date that have focused on possible associations between diet and AAA growth rate.

Alcohol

Inverse associations between consumption of alcohol in moderate amounts and cardiovascular diseases (e.g. myocardial infarction and stroke) have been reported (Mukamal et al, 2003a; Mukamal et al, 2005b; Ronksley et al, 2011a). A light to moderate consumption of alcohol have generally been found to decrease systemic inflammation and oxidative stress (Brien et al, 2011), two components that are of major importance in AAA pathophysiology (Bjorck et al, 2013; Miller et al, 2002; Shah, 1997). More specifically, ethanol has been observed to promote favorable effects on lipid regulation (Mukamal et al, 2005b), while polyphenolic content mostly found in red wine, but also in white wine and beer (Arranz et al, 2012), has been associated with further beneficial effects on systemic inflammation (Estruch et al, 2004), oxidative stress (Estruch et al, 2011a), and endothelial function (Tousoulis et al, 2008).

Only two epidemiological studies have investigated possible associations between alcohol consumption and AAA disease, and results were inconsistent (Tornwall et al, 2001; Wong et al, 2007). Although one of the studies observed a linear trend toward an increased AAA risk across categories of increasing alcohol consumption, the increase in risk observed in the highest category of consumption was not statistically significant. Furthermore, that study was limited to a population free from cardiovascular diseases (Wong et al, 2007). In the other study, an indication of a J-shaped association between alcohol consumption and AAA was observed, although in a population consisting of only male smokers (Tornwall et al, 2001). There is no study that has reported associations for specific types of alcohol (e.g. wine, beer, or spirits).

Comorbidity

AAA is a disease associated with many comorbid states. Most risk factors are commonly shared with those of other cardiovascular diseases (Rodin et al, 2003). *Coronary artery disease* is more frequently observed among those with an AAA, compared with those without (Lederle et al, 2000). *Atherosclerosis* is a well-known causal factor for myocardial infarction and, as previously mentioned, it is also present in a majority of AAA patients, although it is generally not considered a causal factor in AAA development (Golledge et al, 2010). Such statement is further supported by the fact that *diabetes mellitus* has been observed to be inversely associated with AAA prevalence (Lederle, 2012), and with AAA progression (Sweeting et al, 2012). In the Health in Men Study, fasting glucose was inversely associated with AAD in 2859 healthy non-diabetics (Le et al, 2007). Furthermore, *hypertension* and *hyperlipidemia* is more common among AAA patients (Baumgartner et al, 2008; Kent et al, 2010; Lederle et al, 2000; Tornwall et al, 2001; Wong et al, 2007). However, although it has been speculated that hypertension contributes to AAA progression by degrading the aneurysm wall through increased inflammatory activity (De Keulenaer et al, 1998), mean blood pressure was not associated with AAA growth rate in a meta-analysis of 15,475 people under AAA surveillance (Sweeting et al, 2012).

Most probably due to the strong correlation between smoking and AAA (as previously discussed), AAA's are also more common among patients with chronic airway diseases, such as *Chronic Obstructive Pulmonary Disease* (COPD) (Flessenkaemper et al, 2015; Lederle et al, 2000). This is clinically important when deciding treatment method since postoperative survival after AAA repair is reported to be lower in COPD patients (Khashram et al, 2015).

CLINICAL MANAGEMENT

Definition of AAA

There are several available definitions of an AAA, all of which are based on the maximal AAD (Collin et al, 1988; Johnston et al, 1991; McGregor et al, 1975; Sterpetti et al, 1987), and there is an ongoing debate concerning which is the most suitable one. It is, however, clear that a AAA definition needs to be clinically applicable, take into account the variation in AAD due to differences in sex, age, and anthropometric measures, and best predict a condition that eventually will become clinically relevant.

The International Society for Cardiovascular Surgery/Society for Vascular Surgery Ad Hoc Committee defines an arterial aneurysm by an artery diameter 50% larger than what can be expected (Johnston et al, 1991). While such definition takes into account interpersonal changes in AAD, it relies on the assumption that the normal diameter of the artery is known. In 1965, Steinberg and Stein established the normal standard AAD, and concluded that an AAD ≥30 mm was well above average for both men and women and, hence, suggested as a suitable definition separating an ectatic aorta and an aneurysm (Steinberg et al, 1966). McGregor et al confirmed the limit of an AAA as a maximal infrarenal AAD of ≥30 mm approximately ten years later, which is the most commonly used definition to date (McGregor et al, 1975).

Other suggestions to define an AAA is to relate the supra- with the infrarenal abdominal aorta, as this ratio has been found to be the most important predictor of expansion (Sterpetti et al, 1987). Sterpetti et al suggested that a maximal infrarenal abdominal aorta ≥50% larger than the suprarenal aortic diameter was a suitable definition of an AAA (Sterpetti et al, 1987). In turn, Collin et al have suggested a AAA definition as a maximal infrarenal AAD of ≥40 mm, or ≥5 mm larger infra- than suprarenal aortic diameter (Collin et al, 1988).

Given that the AAD among women is smaller than among men, it has been suggested that the definition of an AAA should be smaller in women. In a magnetic resonance imaging study on 70-year-old healthy men and women, authors suggested a definition based on calculations of the mean aortic diameter plus two standard deviations (SD), and/or the mean ratio of the infrarenal aorta to the suprarenal aorta. With such definition, the AAD defining an AAA was suggested to be 30 mm among men, respectively 27 mm among women (Wanhainen et al, 2008c).

Diagnostics

Historically, AAA was diagnosed with abdominal palpation and plain X-ray, techniques that had severe limitations in detecting the disease (Collin et al, 1988; Lederle et al, 1988). Technological advancements since the 1980's have, however, enabled more accurate and noninvasive techniques to detect presence of clinically unknown AAA, such as ultrasound and computed tomography angiography (Gomes et al, 1987).

For practical and economic reasons, and due to a reported sensitivity and specificity as high as 100% if performed by trained ultrasonographers (Lederle et al, 1988; Lindholt et al, 1999), ultrasound has become the most common method for screening and follow-up of infrarenal AAAs. For preoperative planning, however, computed tomography angiography is the preferred imaging modality as it provides more information about the AAA and its surrounding structures (Papanicolaou et al, 1986). However, there has been observed an intra-, as well as an inter-, observer variability for both that modality and ultrasound (Akkersdijk et al, 1994; Ellis et al, 1991; Lederle et al, 1995), and AAA definitions requiring measurement of the suprarenal aorta can be difficult to perform with ultrasound (Ellis et al, 1991; Gomes et al, 1978). Other imaging modalities available, but not recommended, for routine pre-operative planning is magnetic resonance angiography, digital subtraction angiography, duplex ultrasound, and intravascular ultrasound (Moll et al, 2011).

How the aorta should be measured is also a subject of discussion, and depending on which method that is used, different AAA prevalences could be estimated. An antero-posterior measurement, rather than a transverse, is recommended due to its better repeatability (Ellis et al, 1991). There is, however, no recommendation for whether to measure the inner or the outer AAD, and available studies are inconsistent in this matter. For example, the UK Small Aneurysm Trial used external diameter (UKSAT, 1998b), while the Multicentre Aneurysm Screening Study used internal diameter (Ashton et al, 2002), to assess whether the participants harbored an AAA or not. The three most common principles of measurements are the leading edge to leading edge (LELE), the outer to outer (OTO), and the inner to inner principle, all described in Figure 3. Since the LELE-principle showed the highest repeatability of the three methods (Gurtelschmid et al, 2014), it is consensus to use LELE in Sweden (SBU, 2015).
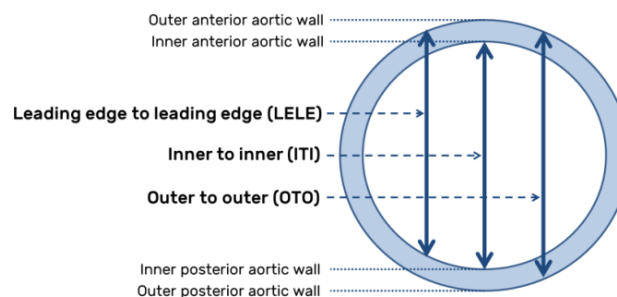

Figure 3. Schematic drawing of the three most common ways of measuring the abdominal aorta to acquire its diameter; leading edge to leading edge, inner to inner, and outer to outer.

Screening

Screening is a method to detect asymptomatic disease by use of a certain test. The intention with screening is to detect a disease in its early stages in order to offer a treatment more effective than if the disease had been allowed to progress further. The World Health Organization (WHO) has defined some basic criterion in order to motivate screening of a disease in a certain population; the disease needs to be easy to detect and represent a common and significant health problem, have serious consequences if left untreated, and the treatment offered should be good and effective (Wilson et al, 1968). A more soft criteria, but nonetheless important, is the issue of cost-effectiveness of the screening program as a whole.

AAA screening

AAA disease is common among the elderly, the mortality rate of untreated AAAs leading to rupture is at least 70% (Acosta et al, 2006; Wanhainen et al, 2008a), and the offered treatment of elective AAA repair is cost-effective and well-established in the modern medical society. Furthermore, ultrasound based screening for the disease is cheap, accurate, safe, and quick. Hence, AAA fulfills all of WHO's criterion to motivate a screening program (SBU, 2015).

Four randomized controlled trials, with 11 to 15 years of follow-up, have investigated whether a AAA screening program is effective; the Chichester Trial in the UK (Scott et al, 1995), the Viborg Trial in Denmark (Lindholt et al, 2002), the Multicentre Aneurysm Screening Study in the UK (Ashton et al, 2002), and the Western Australia trial (Norman et al, 2004). The first three trials provided evidence that ultrasound based screening for AAA among men aged 65 to 74 years is an effective method to reduce AAA-related mortality. In the Western Australia trial, no benefit of AAA screening among men aged 63 to 85 years was observed, which have been attributed to a higher degree of diagnostic activity and treatment of the disease in the control group compared with the control groups of the other three trials. In meta-analyses, AAA-related deaths were 40% to 43% lower in groups invited to screening, compared with non-screened groups (Cosford et al, 2007; Fleming et al, 2005). Furthermore, a 2.7% decrease in all-cause mortality has also been reported (Takagi et al, 2013; Thompson et al, 2012). Other meta-analyses have reported data at mid-term and long-term follow-up (Lindholt et al, 2008; Takagi et al, 2010).

Although not assessed specifically in the randomized trials, the most implemented model of screening is a one-time screening at 65 years of age. The age limit of 65 years has, however, recently been questioned as 18.3% of all patients that presented with a rAAA between 2002 and 2013 in two large hospitals in Finland were younger than 65 years of age when rupture occurred (Laine et al, 2016).

Patients screened with an AAA below the indicated threshold for repair are recommended re-screening as part of surveillance programs, with tighter intervals between investigations the larger the aneurysm (Bown et al, 2013; Thompson et al, 2013). Given the increasing longevity and, thereby, an increased timespan to develop an AAA after the age of 65, it has been suggested that individuals with an AAD 25 to 29 mm at 65 years of age might benefit from rescreening later in life (Crow et al, 2001; Hafez et al, 2008; McCarthy et al, 2003). Results after five years of follow-up of a Swedish screening cohort revealed that 52.5% of participants screened with an AAD between 25 and 29 mm at the age of 65 years, had developed an AAA at 70 years of age (Svensjo et al, 2014).

AAA screening among women

The Chichester trial is the only randomized trial that have included a cohort of women for investigation, and authors failed to observe any benefit of AAA screening among women (Scott et al, 2002). However, the study can be criticized for being underpowered. Furthermore, with low autopsy rates, especially among elderly women, there was a risk that numbers based on official causes of death, as in the Chichester trial, did not detect the correct effects of screening. Among women who passed away after the age of 75 in Sweden in 2014, only 3% underwent autopsy (Socialstyrelsen, 2015). With the current sex-neutral definition of AAA and the low prevalence of the disease among women, general screening for AAA among all women seem to be of negligible impact (Svensjo et al, 2013).

However, studies investigating targeted AAA screening among subgroups of women are scarce, and it has been suggested that smoking women might benefit from such tactic (Moll et al, 2011). Regardless of risk factors, the U.S. Preventive Task Force's AAA screening recommendations do not include women (USPSTF, 2005). The American Society of Vascular Surgery, however, recommends AAA screening among ever-smoking women, and among those with a family history of AAA (Chaikof et al, 2009), while the Medicare Part B covers screening for women with a family history of AAA (Moore, 2007). Of all primary repairs of rAAA in Sweden that were reported in the Swedish National Register for Vascular Surgery (Swedvasc) between 1994 and 2005, 14.3% were performed on women (Wanhainen et al, 2008a).

AAA screening in Sweden

General AAA screening programs were introduced in Sweden in 2006, first in Uppsala County where invitations to a one-time investigation have been sent out to all 65-year-old men. In Uppsala, the first 5 yearly cohorts (men born 1941-1945) are also invited to rescreening at the ages of 70 and 75, as part of a research project. Since 2006, all other Swedish Counties have successively introduced population-based screening programs. The population studied in this thesis lived in the counties of Uppsala, Västmanland, and Örebro. In Västmanland County, invitations have been sent out to all 65-year-old men, and to all women aged ≥65 years with a history of smoking, CVD, family history of AAA, or hypertension, to a one-time AAA screening since 2007 (except for those under AAA surveillance, or with a history of AAA repair). In Örebro County, screening programs were implemented in 2009 when men born 1939 (70 years old), were offered a one-time screening. Since then, AAA screening has been offered to men residing in Örebro County between 65 and 70 years of age, screening two birthyear-cohorts each year. The rate of participation in AAA screening programs for 65-year-old men in Sweden have been reported to range between 77.6% and 85% (Linne et al, 2014; Svensjo et al, 2011). Participants eligible for invitation to screening are identified through the National Population Registry.

In Västmanland County, the maximal infrarenal antero-posterior AAD is measured according to the OTO-principle. That principle was also used in Örebro County up until February 2011, after which the LELE-principle was adopted. In Uppsala County, the AAD is measured according to the LELE-principle.

Intact AAA repair

The basis for elective repair of an asymptomatic, intact AAA (iAAA) is to offer the treatment at a point when the risk of rupture exceeds the operative mortality. Established from two large, randomized multi-centre studies (Lederle et al, 2002b; Powell et al, 2007; UKSAT, 1998b), an AAD of ≥55 mm seems to represent such limit among men. Among women, the risk of rupture is approximately 3 times higher compared with men, for AAAs of the same diameter (Brown et al, 1999). This is the rationale behind the fact that the European Society for Vascular Surgery Guidelines recommend repair in women with an infrarenal AAD ≥52 mm (Moll et al, 2011), and the Swedish Vascular Society at ≥50 mm, even though evidence is lacking. These limits have, however, recently been questioned as 5.6% of men who presented with rAAA in two hospitals in Finland between 2002 and 2013 experienced rupture at an AAD below 55 mm, and 11.5% of rAAAs among women presented below 52 mm (Laine et al, 2016). The annual risk of rupture increases as the aneurysm grows, and Lederle et al assessed an annual risk of 9.4% at an infrarenal AAD between 55 mm and 59 mm, 19.1% between 65 mm and 69 mm, and 32.5% above 70 mm (Lederle et al, 2002a). As rapid growth rate have been correlated with an increased risk of rupture, intervention is also recommended if the annual rate of growth exceeds 10 mm (Moll et al, 2011). However, given that only 95% of ultrasound measurements are within ±5 mm when repeated (Wanhainen A et al 2002), such recommendation can be questioned. The perioperative mortality of iAAA repair ranges from 1.6% to 5% (Greenhalgh et al, 2004; Lederle et al, 2002b; Mani et al, 2011; Prinssen et al, 2004; UKSAT, 1998b; Wanhainen et al, 2008b), and has improved over time (Mani et al, 2013).

It is important to note that the 55 mm limit is assessed from population data, and it is always recommended that each patient's risk of surgery is assessed and balanced against the patient's risk of rupture, expected long-term survival, and the patient's own preferences. Example of factors that affect post-operative survival are comorbidities such as renal or pulmonary dysfunction, and cardiac disease (Khashram et al, 2015; Steyerberg et al, 1995), or female sex, and advanced age (Wanhainen et al, 2008b). Some of iAAA's are repaired due to symptoms (e.g. tender aneurysms, abdominal pain), commonly with semiurgent surgery. The perioperative mortality of urgent repair is reported to be double that of elective iAAA repair (Wanhainen et al, 2008b), although that trend seem to have weakened over time.

As previously discussed, the two available methods for repair of AAAs are open repair, and endovascular aneurysm repair (EVAR), both methods with its advantages and disadvantages compared to the other. Compared with EVAR, open repair is associated with higher perioperative mortality, and morbidity, and longer stay at the hospital and intensive care unit (Greenhalgh et al, 2004; Lederle et al, 2009; Prinssen et al, 2004; Stather et al, 2013). However, there seem to be no differences in long-term survival between the two methods (Stather et al, 2013). EVAR, on the other hand, is associated with a higher degree of re-interventions, aneurysm rupture, and there is, thus, a need for a more close and regular post-operative follow-up (Prinssen et al, 2004; Stather et al, 2013). Furthermore, the use of conventional EVAR can be limited due to aneurysm morphology, such as the width and length of the aneurysm neck, since the surgeon have to be able to secure an adequate proximal landing zone in order for the graft to remain in place and safely exclude the aneurysm from circulation. The proportion of AAAs suitable for conventional EVAR is likely to increase with technological advancements (Garcia-Madrid et al, 2004; Greenhalgh et al, 2004; Prinssen et al, 2004).

Most centers decide which method to use based on which method they are most acquainted with, the aneurysm morphology, and the patient's age and comorbidities. Since 1994, elective iAAA repair in Sweden has increased (Mani et al, 2013), which is most likely explained by the introduction of AAA screening programs, and advancements of the EVAR technology, allowing older and more comorbid patients to be treated (Mani et al, 2013; Mani et al, 2011).

Ruptured AAA repair

The three classic signs of a ruptured abdominal aortic aneurysm (rAAA) are a palpable pulsating abdominal mass, sudden and non-relieving pain in the abdomen, chest, or back, and hypotension or a history of syncope. Due to the hypotensive chock following the loss of blood in to the retroperitoneum, and later in to the abdominal cavity, rAAA is basically almost always fatal without repair (Lindholt et al, 2012), and only one third, approximately, of patients suffering of rAAA will get to the surgical theatre in time (Acosta et al, 2006; Wanhainen et al, 2008a).

With emergency open repair of a rAAA, the 30 day mortality has remained around 40% to 50% for many years (Bown et al, 2002; Egorova et al, 2008; Karthikesalingam et al, 2014), while corresponding mortality rate following EVAR for rAAA has been reported to be around 35% (Edwards et al, 2014; Gupta et al, 2014). However, due to patient selection, it is difficult to compare results between open repair and EVAR in an observational setting. Three RCTs have investigated whether EVAR actually reduces mortality compared with open repair (Desgranges et al, 2015; Powell et al, 2014; Reimerink et al, 2013), all of which have failed to demonstrate any benefit in short term survival. The largest of the three trials, the IMPROVE trial, including 29 vascular centers in the United Kingdom and one in Canada, observed no differences between EVAR (when applicable) and open repair in 30 day, or 1 year, mortality (Powell et al, 2015; Powell et al, 2014). However, an approach with EVAR seemed to offer faster discharge with better quality of life, and was cost-effective, among both men and women (Powell et al, 2015). A recent study comparing outcomes after rAAA repair between England and Sweden reported that the 90-day and 5-year mortality was significantly lower in Sweden (Karthikesalingam et al, 2016). Authors attributed the difference between the countries to the greater use of EVAR in Sweden, and the greater proportion of rAAA repairs being performed in high-volume centers.

As with elective repair of iAAA, it is highly dependable on which center a patient is admitted to if rupture has occurred, whether the patient is going to be treated with EVAR or open repair. In Sweden, open surgery still remain the most common treatment of choice for rAAA, but the use of EVAR have, however, been increasing over the last years (Mani et al, 2013).

AIMS

The overall aims of this thesis were to study associations between modifiable, lifestyle-related factors and risk of AAA. The specific aims were:

- To examine the sex-specific associations between smoking (i.e. smoking status, pack-years smoked, and smoking cessation) and risk of AAA (Study I)

- To examine possible associations between central obesity, as assessed with waist circumference, and total obesity, as assessed with Body Mass Index, and risk of AAA (Study II).

- To examine possible associations between dietary sources of antioxidants – fruit and vegetable consumption – and risk of AAA (Study III).

- To examine possible associations between total consumption of alcohol (ethanol), and specific alcoholic beverages (spirits, wine, and beer), and risk of AAA (Study IV).

- To examine possible associations between comorbidities and modifiable, lifestyle-related factors – obesity, diet, physical activity, smoking, and alcohol consumption – and risk of AAA when screening elderly men (Study V).

PARTICIPANTS AND METHODS

Study population

The five studies of this thesis are based on prospective data from two cohorts of middle aged men and women from Central Sweden; the Swedish Mammography Cohort (SMC) (Study I - IV), and the Cohort of Swedish Men (COSM) (Study I - V). A detailed presentation of the two cohorts is described by Harris et al. (Harris et al, 2013).

The Swedish Mammography Cohort

The SMC was established between 1987 and 1990 when all women born between 1914 and 1948, residing in Uppsala and Västmanland Counties (Figure 4), were invited to a mammography screening program. Together with the invitation, they also received a questionnaire on diet and other lifestyle-related factors. Of the 90,303 women that were invited to participate in the study, 66,651 (74%) responded to the questionnaire. To update the data, and to collect additional information, an expanded questionnaire was sent out in the fall of 1997 to all women still alive and living in the study area. This second questionnaire included questions on ~350 lifestyle-related issues, such as sociodemographic information (e.g. educational level), health status (e.g. comorbidities, medications used), anthropometrics (e.g. weight, length, waist circumference), smoking, physical activity, comorbidities, and a dietary section consisting of a detailed 96-item food frequency questionnaire (FFQ). Of the 56,030 women invited, 39,227 (response rate 70%) returned the questionnaire that was used for baseline exposure assessment in all studies in this thesis that included women (Study I - IV), primarily because information on smoking was not included in the first questionnaire from 1987.

The Cohort of Swedish Men

Simultaneously as the second SMC questionnaire was sent out in 1997, a similar questionnaire (except for some sex-specific questions) was sent out to all men born between 1918 and 1952, residing in Västmanland and Örebro Counties (Figure 4), inviting them to participate in the COSM. Out of the 100,303 men that were invited, 48,850 (49%) returned the questionnaire.

Figure 4. Study area for the Swedish Mammography Cohort (Uppsala and Västmanland Counties) and the Cohort of Swedish Men (Västmanland and Örebro Counties).

Exclusions

The total population size investigated in the studies of this thesis included 84,890 men and women from the 1997 SMC and COSM. Each study was subject to specific inclusion critera, and the specific exclusions from the source population to obtain the study population in each of the studies are presented as a flowchart in Figure 5. In brief, men and women with erroneous or missing personal identification number, or with a history of cancer (except for non-melanoma skin cancer) or AAA (diagnosis of iAAA, rAAA, and AAA repair) were excluded from further analyses in all of the five studies included in this thesis.

For analyses on smoking status, participants with missing information on smoking (i.e. smoking status, pack-years smoked among ever smokers, and years since smoking cessation among past smokers) were excluded (Study I). For analyses on anthropometrics, participants with missing information on those variables (i.e. BMI and waist circumference), and those with a BMI or waist circumference <1st or >99th percentile for each sex, were excluded (Study II). For analyses on diet, participants with an implausible energy intake were excluded (Study III and V). Exclusions were made of those with missing information on fruit and vegetable consumption in Study III, and of those with missing information on alcohol consumption status in Study IV. Last, for the analyses of lifestyle-related factors associated with AAA detected at screening (Study V), only men screened between 65 and 75 years of age were included. Furthermore, analyses were perfomed among a subgroup of those screened where the exact AAD was registered, as the exact diameter was not registered among 5706 participants with an AAD <25 mm.
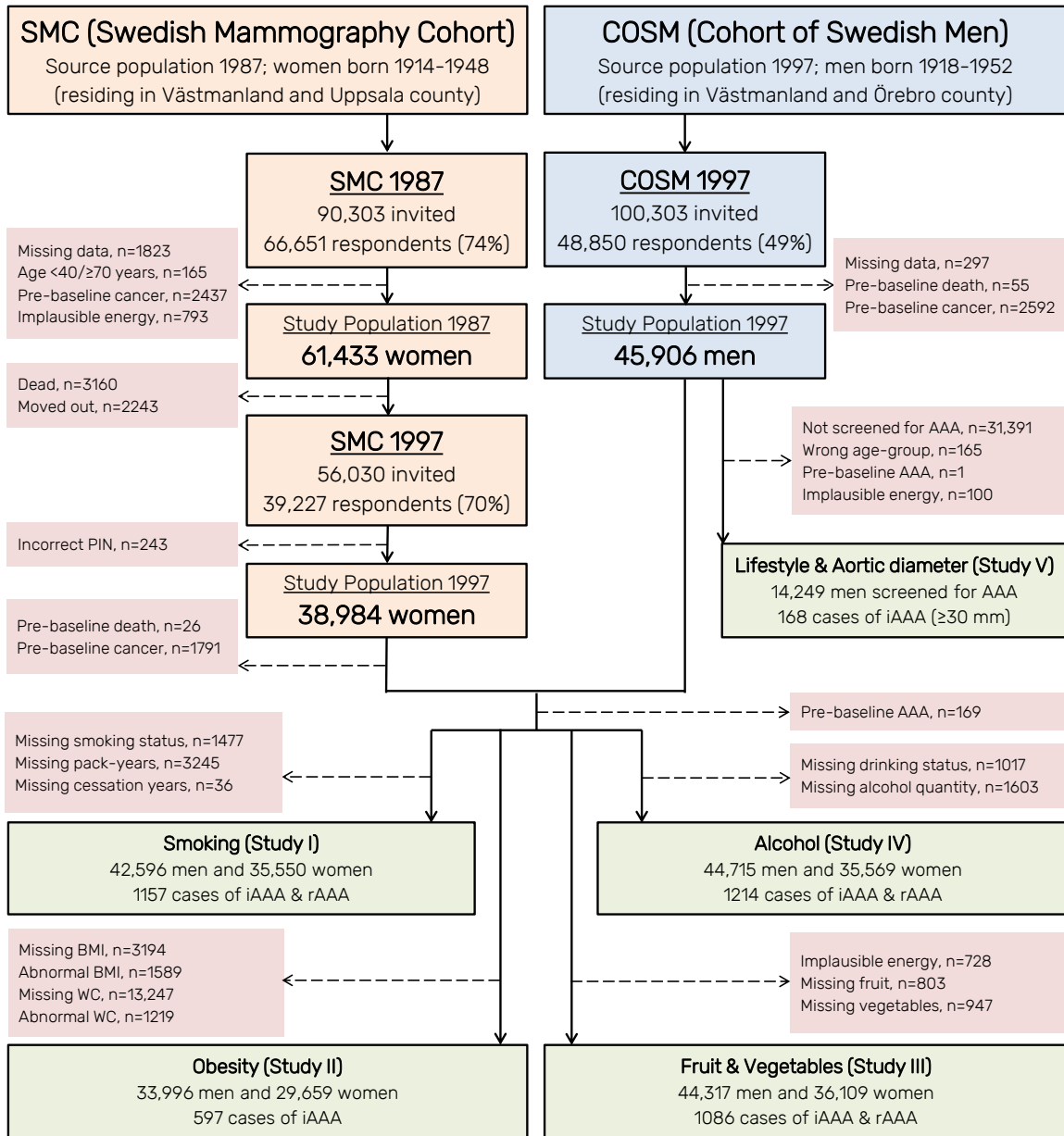
Figure 5. Source population, exclusions, and study population for Study I-V.
COSM indicates Cohort of Swedish Men; SMC, Swedish Mammography Cohort;
AAA, Abdominal Aortic Aneurysm (iAAA and rAAA, intact and ruptured AAA);
BMI, Body Mass Index; WC, Waist circumference; PIN, Personal Identification Number

Representativeness of the cohorts

Although participants of the two cohorts tended to be slightly younger and less educated at baseline than the Swedish population, the SMC and the COSM are considered representative of the Swedish population at time of data collection in 1997. Comparisons of age-distribution, educational level, proportion of obese people, and proportion of current smokers, between the Swedish population in 1997 (Official Statistics Sweden, 1997), the original 1997 cohorts, and the analytical cohorts in the studies of this thesis, are reported in Table 1A for women, and Table 1B for men. The proportion of current smokers in the two cohorts were also similar to the proportion of daily smokers in a national survey on living conditions in 1996/97 performed by Official Statistics Sweden (Official Statistics Sweden, 1997) between the ages 45 and 74 years. Among men aged ≥75 years, there were a larger proportion of current smokers in the COSM than in the Swedish population.

Table 1A. Age distribution, educational level and body mass index among women in the SMC

	Analytical SMC 1997 population in Study I-IV*				Original SMC -97	Population 1997†
	I	II	III	IV		
Age group (years)						
Total no.	35 550	29 659	36 109	35 569	38 984	1 633 520
48–54	29.4	28.7	29.5	29.8	28.5	27.6
55–59	18.2	18.2	18.3	18.4	17.9	15.0
60–64	14.7	14.6	14.6	14.7	14.5	12.7
65–69	13.4	13.9	13.4	13.3	13.5	12.7
70–74	12.1	12.5	12.1	12.0	12.4	12.7
75–79	9.5	9.6	9.5	9.3	10.1	12.1
80–83	2.7	2.5	2.6	2.5	2.9	7.3
Education, ages 48–74 years ‡						
Total no.	31 208	26 073	31 740	31 370	33 914	1 316 743
≤12 years	78.8	79.0	78.8	78.6	78.9	78.7
>12 years	20.9	20.7	20.9	21.1	20.5	19.9
Body mass index (>25 kg/m^2), by age groups §						
45–54 years	37.5	35.7	37.3	37.4	37.6	38.8
55–64 years	45.5	44.4	45.5	45.4	45.7	47.4
65–74 years	49.6	48.6	49.6	49.5	49.7	52.0
75–84 years	42.8	41.9	42.8	42.7	42.9	42.3
Current smokers, by age groups ‖						
45–54 years	26.8	25.6	26.0	26.0	26.1	30.6
55–64 years	21.2	20.0	20.6	20.7	20.8	21.5
65–74 years	13.7	12.5	13.2	13.4	13.4	16.5
75–84 years	8.3	7.8	7.9	8.0	7.9	7.7

Values are percentages unless indicated otherwise; percentages may not add up to 100 owing to missing values.
SMC indicates Swedish Mammography Cohort.
*) Analytical cohorts obtained after exclusion of those with a history of abdominal aortic aneurysm or cancer, and those with missing data on primary exposures (see Figure 4 for a detailed description of exclusions).
†) Data from Official Statistics Sweden (OSS).
‡) Educational level reported for those aged 74 years or less as there were no available data from OSS for older women.
§) Proportion of overweight (Body Mass Index >25 kg/m^2) people within each age-group.
‖) Proportions of current smokers within each age-group are reported for the cohorts, while corresponding proportions of daily smokers are reported for the population.

Table 1B. Age distribution, educational level and body mass index among men in the COSM

	Analytical COSM 1997 population in Study I-V*					Original COSM -97	Population 1997†
	I	II	III	IV	V		
Age group (years)							
Total no.	42 596	33 996	44 317	44 715	14 249	45 906	1 594 952
45–49	16.6	15.8	16.2	16.1	7.6 ‡	15.9	19.5
50–54	19.6	18.9	19.1	19.1	45.1 ‡	18.8	20.8
55–59	16.4	16.1	16.2	16.1	33.3 ‡	15.9	15.6
60–64	13.3	13.2	13.1	13.1	11.4 ‡	13.1	12.5
65–69	13.9	14.2	14.0	14.0	2.6 ‡	14.1	11.6
70–74	11.6	12.3	12.1	12.2	-	12.4	10.8
75–79	8.6	9.5	9.4	9.5	-	9.9	9.2
Education, ages 48–74 years §							
Total no.	38 914	30 756	40 144	40 455	14 249	41 382	1 448 585
≤12 years	82.0	82.2	82.2	82.3	80.4	82.3	77.1
>12 years	17.7	17.6	17.5	17.4	19.4	17.3	21.0
Body mass index (>25 kg/m^2), by age groups ‖							
45–54 years	54.6	54.2	54.5	54.5	56.4	54.5	57.2
55–64 years	59.1	58.6	59.0	59.0	58.6	59.1	60.3
65–74 years	56.4	56.2	56.5	56.7	63.2	56.8	57.0
75–84 years	47.3	47.5	47.1	47.3	-	47.5	43.0
Current smokers, by age groups #							
45–54 years	27.9	26.2	27.5	27.6	24.2	27.7	23.2
55–64 years	23.5	22.3	23.5	23.5	20.2	23.7	22.8
65–74 years	21.4	20.9	21.8	22.1	16.1	22.4	17.2
75–84 years	20.3	19.8	21.2	21.9	-	22.1	13.4

Values are percentages unless indicated otherwise; percentages may not add up to 100 owing to missing values.
COSM indicates Cohort of Swedish Men.
*) Analytical cohorts obtained after exclusion of those with a history of abdominal aortic aneurysm or cancer, and those with missing data on primary exposures (apart from Study V, see Figure 4 for a detailed description of exclusions).
†) Data from Official Statistics Sweden (OSS).
‡) Participants in Study V only included men screened for AAA between 65 and 75 years of age, mean 13 years after baseline, explaining the non-representative distribution of age in this analytical cohort.
§) Educational level reported for those aged 74 years or less as there were no available data from OSS for older men.
‖) Proportion of overweight (Body Mass Index >25 kg/m^2) people within each age-group.
#) Proportions of current smokers within each age-group are reported for the cohorts, while corresponding proportions of daily smokers are reported for the population.

Methods

Assessment of exposures

Education
Information on education was based on self-reported data solicited in the questionnaire. When compared with the Swedish population in 1997, participants in the SMC (Table 1A) and the COSM (Table 1B) tended to have a slightly lower proportion of people with a university degree.

Smoking
Participants reported smoking status (never, past, or current smokers) at baseline in the 1997 questionnaires. The daily consumption of cigarettes was reported for several periods in life: ages 15 to 20 years, each decade thereafter, and at baseline. One pack-year was defined equivalent to 20 cigarettes per day during one year. There has been no specific validity assessment of smoking status in the SMC or the COSM. In a systematic review of studies validating self-reported smoking habits against saliva cotinine measures, a trend towards underestimation was reported (sensitivities ranged from 78% to 97%) (Gorber et al, 2009). The proportion of current smokers among men aged ≥75 years in the COSM 1997 was larger (22.1%) than the proportion of daily smokers in the general population (13.4%) (Table 1B). In other age-groups, and among women, the corresponding proportions were comparable with those in the general Swedish population in 1997 (Table 1A and Table 1B).

Obesity
In the questionnaires, participants reported baseline weight and waist circumference, as well as the height at the age of 20 years. Body mass index was calculated as weight (kg) divided by height squared (square meter). Swedish men and women tend to overestimate height and underestimate weight (Nyholm et al, 2007), but the validity of self-reported BMI compared with clinical measures was high (r = 0.9) (Kuskowska-Wolk et al, 1989). The proportion of participants in the two cohorts with a BMI >25 kg/m^2 was comparable with that of the Swedish population in 1997 (Table 1A and Table 1B). Waist circumference has not been validated in these cohorts, but in a validation study of the Health Professionals Follow-up Study and the Nurses' Health Study, the correlation between self-reported and technician measured waist circumference was reported as high (r = 0.9 for men and women) (Rimm et al, 1990).

Physical activity

In the questionnaire, participants reported time spent walking or bicycling for everyday transportation purposes for several intervals in life (at 15, 30 and 50 years of age, and at baseline). The questionnaire also gathered information on leisure-time exercise for the same time periods of life. The Spearman rank correlation coefficient between the questionnaire and activity records among 111 men, asked to report two seven-day activity records 6 months apart, was 0.4 for combined walking/bicycling (Norman et al, 2001).

Diet

Information on diet was assessed with a 96-item FFQ. The average frequency of consumption during the previous year was reported by use of eight predefined categories, ranging from never to ≥3 times per day. Foods that are commonly consumed, such as dairy products and bread, were reported in open ended questions as servings per day, or week. The questionnaire has been validated for nutrients (Messerer et al, 2004), and the average Spearman correlation coefficients between estimates from the dietary questionnaire and the mean of four 24-h recall interviews of 248 men, aged 40 to 74 years, were 0.65 for macronutrients and 0.62 for micronutrients (Messerer et al, 2004). Food composition data from the Swedish National Food Administration were used to calculate energy intake (Bergstrom et al, 1991).

In Study III, daily average consumption of total fruit, and total vegetables, were the primary exposures of interest. This was calculated after converting the responses to average daily consumption of each specific fruit and vegetable, and then summing the daily average consumption of all individual fruits (oranges and other citrus fruits, apples and pears, bananas, berries, and other fruits) and vegetables (carrots, beets, lettuce and leafy greens, cabbage, cauliflower, broccoli and Brussels sprouts, tomatoes and tomato juice, peppers, spinach, onions and leek, garlic, and green peas). When aggregating the specific items, missing values for an individual food were assumed to mean no intake of that item (Hansson et al, 2000). When comparing the FFQ and four 1-week weighted diet records, the Spearman correlation coefficients ranged from 0.6 (apples, pears) to 0.7 (oranges, other citrus fruits) for fruits, and from 0.4 (tomatoes) to 0.6 (spinach) for vegetables (Wolk A, unpublished data).

In Study V, a healthy diet score, defining the overall diet quality based on guidelines and current knowledge (Michels et al, 2002), was used as one of the primary exposures. The score included foods beneficial for cardiovascular health (Hu et al, 2002; Lichtenstein et al, 2006; WHO, 2002), and added up to a maximal score of 25. A food score of one was assigned for 1 or more servings per week of all individual fruits (apples and pears, bananas, citrus fruits, and berries), vegetables (spinach, lettuce and green salad, cabbage, cauliflower, broccoli and Brussels sprouts, carrots, beetroots, tomatoes and tomato juice, sweet pepper, green peas, and mixed vegetables), legumes, nuts, low-fat dairy products (reduced-fat milk, reduced-fat cultured milk/yogurt), whole grains (oatmeal, whole grain bread, crisp/hard bread), and fish (herring/mackerel, salmon/whitefish/char, and cod/saithe/fish fingers).

Alcohol

In the FFQ, participants reported alcohol consumption status (never, former, current drinker), frequency of consumption of specific alcoholic beverages, and amounts consumed at a single occasion. Frequency during the past year was reported by use of eight predefined categories, ranging from never to ≥3 times per day, while amount of beer, wine, and spirits was reported in open-ended questions. The questionnaire has been validated for alcohol intake by use of 14 interviews (each month during one year on randomly chosen days) that assessed 24-hour recall of intake among 248 study participants. The Spearman rank correlation coefficient was 0.81 (Messerer et al, 2004).

In Study IV, in which alcohol consumption was the primary exposure of interest, missing values of frequency or amounts among current drinkers were assumed to mean the least possible consumption (i.e. 0–1 times/month for frequency and one standard glass for the amount). If both frequency and amount was missing for a beverage, a null consumption was assumed (Di Giuseppe et al, 2012). After average weekly frequency of beverages had been calculated, frequency and amount was multiplied to obtain the average number of standard glasses consumed per week. One standard glass (12 grams of ethanol), hereby referred to as a glass, was considered equal to 15 cl of wine, 8 cl of strong wine, 66 cl of class I beer (<2.25%), 50 cl of class II beer (2.25–3.5%), 33 cl of class III beer (≥3.5%), or 4 cl of spirits. Glasses of beer were obtained by combining glasses of class I, II, and III beer, while glasses of wine were obtained by combining glasses of wine and strong wine.

Comorbidity

Information on comorbidities (i.e. diabetes, hypertension, hypercholesterolemia, and cardiovascular diseases [CVDs; angina pectoris, myocardial infarction, ischemic stroke, heart failure, and peripheral artery disease]) were obtained by linkage to the Swedish National Patient Register (NPR) and the Swedish National Diabetes Register (NDR), and supplemented with self-reported data from the questionnaires (including hypertension and hypercholesterolemia).

In Sweden, all diagnoses leading to hospitalization are mandatory to enter as discharge diagnoses and registered in the NPR. This register has had a nearly complete coverage of the Swedish population since 1987 (Ludvigsson et al, 2011), and includes information on both primary and secondary diagnoses. Since 2011, it also includes visits from both public and private caregivers.

In validity assessments (as reviewed by (Ludvigsson et al, 2011)), the proportion of correct diagnosis for above mentioned comorbidities were as follows; angina pectoris, 95%; myocardial infarction, 98% to 100%; stroke/transient ischemic attack, 98.6%, vascular interventions [for lower limb ischemia], 99.8%; heart failure, 88%; and diabetes mellitus, 79%. Furthermore, the sensitivity was as follows; myocardial infarction, 77% to 91.5%; ischemic stroke, 84.2% to 98%; angina pectoris, 43.9%; hypertension 8.8% to 13.7%; lipid disorders, 10.2%; diabetes mellitus, 23.3% to 80%. The sensitivity of heart failure and peripheral artery disease in the NPR is not known.

In order to improve sensitivity of diabetes mellitus diagnosis, participants of the cohorts were linked to the NDR. The NDR, initiated in 1996, retrospectively assess information from patient visits, and year of diabetes onset, each year. The coverage of the NDR (Guðbjörnsdóttir et al, 2014) is estimated to be nearly complete in Västmanland and Örebro County, based on expected prevalence of diabetes. When validated against the Swedish Prescribed Drug Register, the NDR covered >90% of individuals on diabetes medication aged 50 to 80 years. In Uppsala County, the coverage of the NDR is reported to be 62% based on expected prevalence of diabetes, respectively ~75% if compared with the Swedish Prescribed Drug Register (Guðbjörnsdóttir et al, 2014).

Thus, it is likely that not all participants with comorbidity are identified, especially not participants with angina pectoris, hypertension, or hyperlipidemia. However, participants with more severe cardiovascular diseases (e.g. myocardial infarction or ischemic stroke), and diabetes, are most likely identified through the NPR and the NDR.

Assessment of AAA and follow-up of the cohorts

In Study I-IV, AAA cases were identified through linkage of the cohorts to three national Swedish Registers; the NPR, the Swedish Cause of Death Register (CDR), and the Swedish National Register for Vascular Surgery (Swedvasc). Thus, cases were clinical events and not based on routine screening of all study participants. In Study V, the three registers were used to identify history of AAA prior to baseline, while AAA as outcome was based on ultrasound measurements of all men that had participated in AAA screening between 65 and 75 years of age.

The National Patient Register and the Cause of Death Register

Hospital discharges, surgical procedures, and deaths due to AAA were identified by linkage to the NPR and the CDR, by use of the International Classification of Diseases (eight, ninth and tenth revision [ICD-8, 9, and 10]). Surgical procedures are registered according to the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures. AAA diagnosis has not been specifically validated in the NPR. However, the register has a high validity in general (Nilsson et al, 1994), and a nearly complete hospitalization coverage of the Swedish population since 1987 (Ludvigsson et al, 2011). In total, surgical procedures have been reported as incorrect in 2%, and missing in 5.3%, of the records (Nilsson et al, 1994).

The CDR annually collects causes of death since 1961, which are registered according to the ICD-8, -9, and -10. Quality of the data varies, mainly with the quality and thoroughness of the examination at time of death, and how accurately the physician has reported diagnoses on the death certificate. Furthermore, time trends may be affected by changes in diagnostic methods, medical concepts, vocabulary, classification systems, and processing methods. A decline in autopsies entails a higher risk that causes of death are incorrectly registered. Since the beginning of the 1970's, autopsy rates have generally declined; from 50%, to 11% in 2014. Furthermore, the rate of autopsies performed is also very age- and sex-dependent, and have declined from 22% in 1997 to 15% in 2014 among all men, and from 13% to 7% among all women. Corresponding proportions among men aged >75 years have declined from 13% to 6%, respectively 9% to 3% among women aged >75 years. In 2014, 164 men and 80 women were assigned AAA as cause of death in Sweden (Socialstyrelsen, 2015).

Swedvasc

Since the NOMESCO classification only classifies type of procedure performed, linkage of the cohorts to Swedvasc further enriched information on rupture status and aneurysmal localization of repairs. The register was founded in 1987 and covers all hospitals with a vascular service in Sweden since 1994. In this register, AAA is registered in a specific module for treatment of aortic diseases, and has been reported to cover 93.1% of all AAA repairs (Troeng et al, 2008). A recent validation study reported that the external validity of Swedvasc was 98.8% for AAA repair when comparing Swedvasc with the NPR (Venermo et al, 2015). In the COSM and the SMC, 91.4% of AAA repairs registered in Swedvasc between 1 January 1998 and 31 December 2011, were registered in the NPR (361 out of 395), while 69.4% of AAA repairs registered in the NPR during the same time period were registered in Swedvasc (361 out of 520).

All first-time events due to intact or ruptured AAA in the infra- or suprarenal abdominal aorta, and in the common or internal iliac arteries were classified as cases in Study I, III, and IV. In Study II, events due to intact disease were classified as cases. Codes used to identify AAA are displayed in Table 2.

Table 2. Identification codes used to identify AAA in the National Patient Register, the Cause of Death Register, and the Swedish Register for Vascular Surgery (Swedvasc)

Source	iAAA	rAAA
ICD-10	I71.4	I71.3
ICD-9	4414	4413
ICD-8	4412	4412
Swedvasc	iAAA	rAAA
Infrarenal surgery	PDG10-99	PDG10-99
Infrarenal stent	PDQ10-99	PDQ10-99
Suprarenal surgery	PCG10	PCG10
Suprarenal stent	PCQ10	PCQ10

AAA indicates Abdominal Aortic Aneurysm; ICD-8, 9, and 10, International Classification of Diseases (eight, ninth and tenth revision); iAAA, intact Abdominal Aortic Aneurysm; rAAA, ruptured Abdominal Aortic Aneurysm; Swedvasc, the Swedish National Register for Vascular Surgery.

Screening cohort

In Study V, all men that had undergone AAA screening between 65 and 75 years of age were included for analyses of lifestyle-related factors associated with AAD, and with hazard of AAA.

AAD was assessed with ultrasound examination of all men that had participated in AAA screening between 65 and 75 years of age. To account for differences in AAD depending on which of the two methods that were used to measure the abdominal aorta (i.e. the OTO- or the LELE-principle) in Västmanland and Örebro County, 2 mm were subtracted for all diameters registered with the OTO-principle prior to data analysis (Gurtelschmid et al, 2014). An AAA was defined as a maximal infrarenal AAD of ≥30mm.

Representativeness of AAA

When combining data from the three registers to identify AAA in the COSM and the SMC in Study I-IV, the incidence of AAA between 1998 and 2005 corresponded to the incidence in Mid-Sweden (the same study area) between 1990 and 2005 reported by Hultgren et al in a nationwide population-based study (Hultgren et al, 2012). When data were standardized for the same distribution of age (i.e. weighted for the distribution of the yearly population average in Mid-Sweden in the age categories ≤59, 60-69, 70-79, and ≥80 years), the incidence of AAA per 100.000 person-years was 85.6 in the COSM, and 31.8 in the SMC. Corresponding incidences per 100.000 person-years reported by Hultgren et al was 86.5 among men, respectively 26.8 among women. Regarding the different time interval for the comparison of incidences with that study (1990 to 2005 compared with 1998 to 2005), Hultgren et al reported no significant change in incidence over the study period.

Although no validation of the screening data in Study V has been performed, the reported sensitivity and specificity of ultrasound investigation for AAA has been reported as high as 100%, if performed by trained ultrasonographers (Lederle et al, 1988; Lindholt et al, 1999). The AAA prevalence among men screened for AAA between 65 and 75 years of age in the COSM was 1.2%, which is lower than the 1.7% reported in a population-based screening study of 65-year-old men in Central Sweden (Svensjo et al, 2011).

Statistical analyses

In Study I-V, Cox proportional hazard regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI's) for the associations between lifestyle-related exposures and AAA hazard. Specifically, exposures focused on for each of the studies were: smoking status, pack-years smoked and time since smoking cessation (Study I), abdominal- and total adiposity (Study II), daily fruit and vegetable consumption (Study III), alcohol consumption and specific alcoholic beverages (Study IV), and comorbidities and lifestyle-related exposures (Study V).

The Cox proportional hazard regression model was introduced by David R. Cox in 1972 (Cox, 1972), and is now one of the most widely spread methods to analyze survival data. The HR's estimated by the method measures the extent to which a variable multiplicatively increases or decreases the event rate. The model is often referred to as semi-parametric since the modelling of the mathematical function is parametric, but assumes no shape for the baseline hazard. However, the model assumes that the hazards of compared covariates are proportional over time (e.g. the HR's should not change over follow-up time). In the light of this thesis, AAA case ascertainment in Study I-IV may change over time given the introduction of AAA screening during follow-up (i.e. if the exposure of interest was non-differentially misclassified, further discussed in *Methodological considerations; Misclassification of cases*).

The three most powerful diagnostic tools to assess proportionality of hazards are the (weighted) scaled Schoenfeld's residuals test (Grambsch et al, 1994) and the linear correlation test (Harrell, 1986), which test an association between residuals and time (indicating a bad fit), and the time-dependent covariate test (Cox, 1972) which tests whether the HR is constant over time or not. Alternatives to address non-proportionality are to split the follow-up time, abandon the model in favor of some other, or by fitting the non-proportional covariate in a stratified model, allowing the covariate to be modeled without the constraint of proportionality. However, a stratum covariate must be categorical, and is only suitable for covariates with no primary interest since no estimated effect size for such covariate is provided. In Study II and III, sex was controlled for as a stratum variable to allow for different baseline hazard rates, and in the other studies, men and women were analyzed separately. When scaled Schoenfeld's residuals were regressed against survival time to evaluate the assumption of proportional hazards in the final models of the five studies of this thesis, no violation of such assumption could be observed.

Time in survival analyses can be modeled in different ways, with the most common being the time from which the participant enter the study, until the time for which the participant either experience the event of interest, or experience some other event after which he/she can no longer develop the event of interest (i.e. censoring). Another way of defining the timescale, which is becoming more common, is to define it on the age-scale, allowing the participant to enter the study on his/her baseline age, to be followed-up until the age at which he/she experiences the event, or is censored (Cheung et al, 2003; Cologne et al, 2012; Thiebaut et al, 2004; Westreich et al, 2010).

In the studies of this thesis, the study baseline was set to 1 January 1998, and participants were allowed to accrue follow-up time from baseline until the date of experiencing the event of interest (i.e. incident diagnosis of iAAA or rAAA, or AAA repair), or the date of censoring (i.e. death, or 31 December 2010 [Study II], 31 December 2011 [Study III], or 31 December 2012 [Study I and IV]), whichever came first. In Study V, attained age was used as timescale when analyzing hazard of AAA, and participants were allowed to accrue follow-up time from 1 January 1998 until date of screening.

In Study V, possible relationships between lifestyle-related exposures and mean AAD at time of screening were investigated by modelling a linear regression model with AAD as dependent variable.

All statistical tests in the studies included in this thesis were two-sided, and P-values <0.05 were considered statistically significant. Analyses were performed with Stata® version 12.1 (Study I-IV), and version 13.1 (Study V) (StataCorp LP, College Station, Texas, USA).

Modelling of exposures and covariates

Age was flexibly modeled using restricted cubic splines in Study II and III, and stratified into seven 5-year categories in Study I and IV. In Study V, analysis of AAA hazard used attained age as time-scale, while analyses of AAD were adjusted for age at screening.

Educational level was adjusted for in three levels in Study I-IV (primary school, high school, university), while primary school and high school were combined into one category in Study V.

The WHO classification was used for categorization of obesity based on waist circumference for men (<94, 94 to 101.9, and $\geq$102 cm) and women (<80, 80 to 87.9, and $\geq$88 cm) separately (Study I-V), and BMI (normal <25 kg/m^2; overweight 25–29.9 kg/m^2; obese $\geq$30 kg/m^2) (Study I) (WHO, 2000). In Study V, BMI and waist circumference were categorized as binary variables (waist circumference $</\geq$ 94 cm, and BMI $</\geq$25 kg/m^2).

In Study I, smoking status was categorized into never smokers, former smokers divided by years since cessation ($</\geq$20 years), and current smokers divided by numbers of pack-years smoked ($</\geq$20 pack-years). Continuous analyses of pack-years smoked were adjusted for years since cessation, and vice versa, in that study. In Study II and III, smoking status was modeled according to status and pack-years smoked (never, current/former with $</\geq$20 pack-years), while in Study IV and V, ever smokers were divided by the median of pack-years smoked (current with $</\geq$25 pack-years [men], and $</\geq$20 pack-years [women], former with $</\geq$15 pack-years [men] or $</\geq$10 pack-years [women]).

Alcohol consumption was modeled according to the gender-specific quartiles of total alcohol consumption (grams/week) in Study I to III. In Study IV, the exposure was categorized as never, former, or current drinkers (<2; 2–3; 4–6; 7–13; or ≥14 glasses/wk for men, and <1; 1; 2–3; 4–7; or ≥7 glasses/wk for women). In analyses of specific alcoholic beverages among current drinkers, men were grouped into four categories depending on glasses of beverages consumed per week (<1, 1; 2–3; or ≥4), while women were grouped into three categories (never; <1; or ≥1 for beer and spirits, and <1; 1–3; or ≥4 for wine). Never and past drinkers were not included in dose-response analyses of current drinking, or in analyses of specific beverages, to account for potential bias related to characteristics of never drinkers or sick quitters (Study IV). In Study V, a consumption of ≥/< than 1 glass/day separated current drinkers into two categories, while never and former drinkers were combined into one category.

Physical activity was adjusted for in Study III and V, and categorized according to time spent walking or bicycling each day (<20; 20-40; >40 minutes). "Almost never" was also included as category in Study V.

Studies including dietary exposures were adjusted for total energy intake (kcal/day), with participants divided by the quartile distribution of intake in the study population in Study III, and as a continuous variable in Study V. In Study I, III, and IV, multivariable analyses were adjusted for fruit consumption (servings per day in quartiles), while analyses in Study III were further adjusted for fish consumption (<1; 1-2; 2-3; >3 servings/week), and quartiles of vegetables (servings/day), red and processed meat (servings/day), and whole grains (servings/day). Analyses in Study V were adjusted for healthy diet score in approximate tertiles (food score of ≤8, 9-12, ≥13).

In all studies of this thesis, comorbid diseases were modelled as binary variables.

Modelling of continuous variables

The continuous exposures in Study I (waist circumference), II (fruit consumption), III (pack-years smoked among ever smokers, and years since cessation among former smokers), IV (alcohol consumption), and V (BMI and pack-years smoked) were flexibly modeled with restricted cubic splines.

When investigating a continuous exposure, one can include a simple continuous variable in the statistical model. By doing so, one assumes a linear relationship with the outcome, and a common way of relaxing this assumption is to categorize the variable. In turn, such method assumes a step function shape for the association, and ignores within group variation of risk of the outcome. Furthermore, the subjective choice of cut-off may have an impact on observed results and its interpretations (Greenland, 1995a; Greenland, 1995c; Royston et al, 2006).

To avoid the potential loss of information inherited by categorizing a variable, spline transformation can be utilized to model continuous covariates (Greenland, 1995b; Marrie et al, 2009; Royston et al, 1999; Steenland et al, 2004). A spline transformation splits the continuous exposure over its distribution in the study population into a predefined number of intervals at so called knots (Durrleman et al, 1989). In the five studies of this thesis, we applied three knots at fixed percentiles (10th, 50th, and 90th) of the distribution to model continuous covariates. Most commonly, each interval is then modeled with cubic polynomial functions (*cubic splines*), constrained to join at the knots' location, and can be restricted to be linear before the first, and/or after the last, knot (*restricted cubic splines*). Since both tails of the function were restricted in the studies of this thesis, departure from the assumption of linearity could be assessed by testing whether the coefficient of the second spline transformation was equal to zero. An overall association could be assessed by testing whether the coefficients of the two spline transformations were jointly equal to zero. The procedure is easily accomplished by statistical software, and has been summarized by Orsini and Greenland (Orsini et al, 2011).

Modelling of missing data

In almost all epidemiological research, especially in large-scale cohorts with thousands of participants, data is missing. If such data are handled inadequately, it can lead to biased results in the statistical analyses. Missing data can be classified according to Little and Rubin (Little et al, 2002) into three separate categories; 1) missingness that is not dependent on observed or unobserved data (missing completely at random [MCAR]), 2) missingness that is only dependent on observed data (missing at random [MAR]), and 3) missingness that is dependent on unobserved data (missing not at random [MNAR]). For example, in the light of this thesis, data on BMI could be MAR if participants with low physical activity are less likely to report their weight, but the data could also be MNAR if individuals with high BMI are less likely to report their weight. By merely analyzing observed data, distinguishing if the data are MAR or MNAR is not possible, although it becomes more plausible to assume that data are MAR if more explanatory variables are included in the model.

One way of handling missing data is to add it as a separate category (indicator category) for each covariate, while performing complete case analyses is another (where participants with missing data are excluded). Results from the two models can be compared to evaluate the potential impact of missing data.

Another more refined approach to handle missing data is multiple imputation (Rubin, 1987) – a statistical technique that has become increasingly popular (Harel et al, 2007; Horton et al, 2007). Multiple imputation estimates a number of individual datasets with plausible values for the missing data based on the distribution of the observed data in the study population. The datasets are then analyzed separately, and finally combined to obtain overall estimates. In the standard case, multiple imputation assumes that the missing data are MAR.

In larger sets of data, missing data is often present for several variables. An approach to generate imputations in this case is by basing one imputation model on each variable containing missing data. This approach is called multiple imputation by chained equations (MICE). MICE starts by filling in missing values by random sampling from the observed values. The first variable with missing data is then regressed on all other variables, restricted to participants with observed data on that variable, producing a posterior set of predicted values. Missing values are then replaced by simulated draws from the corresponding posterior predicted distribution. Since MICE impute all data based on its own individual imputation model, it can handle different types of variables (e.g. ordinal, nominal, binary, and continuous data). The process is repeated in cycles on all variables containing missing data.

Cycles are then usually repeated several times to stabilize the estimations and result in a single imputed dataset. The whole procedure with multiple cycles is, in turn, repeated multiple times to result in multiple imputed data sets. Although no consensus exists on how many datasets should be imputed for a certain set of original data, a commonly used rule of thumb is to produce at least as many datasets as the overall proportion of missing data in the original dataset. MICE is accomplished by statistical software, and has been summarized by White et al. (White et al, 2011).

In Study I-IV, we included missing data as indicator variables in the statistical models; however, results did not differ when comparing with the complete set of data. As the proportion of participants with missing data on one variable or more was 31% in Study V, MICE with 40 imputed datasets were used to account for missing data in that study. Results of the imputed data did not differ from models were indicator variables were used, or from complete case models. The proportions of missing data for each variable of interest, for each of the five studies included in this thesis, are reported in Table 3.

Table 3. Proportions of missing data for each variable of interest, for each of the five studies

	Analytical population in Study I–V*				
	I	II	III	IV	V
Total no. of participants	78 146	63 655	80 426	80 284	14 249
Total missing					
≥1 variables	19.2	6.8	28.9	21.9	31.2
≥2 variables	1.5	1.5	6.5	2.9	7.3
Missing on specific variables					
Education	0.3	0.3	0.2	0.4	0.2
Body Mass Index	–	0.0	–	–	3.3
Waist Circumference	17.2	0.0	17.2	17.4	18.9
Smoking status	0.0	1.4	1.5	1.5	1.2
Pack-years smoked	0.0	4.6	5.2	5.2	3.6
Alcohol consumption	2.7	2.3	2.4	0.0	1.0
Physical activity	–	–	8.5	–	9.5
Fruit consumption	1.3	–	0.0	1.0	–
Vegetable consumption	–	–	0.0	–	–
Meat consumption	–	–	0.4	–	–
Fish consumption	–	–	1.3	–	–
Wholegrain consumption	–	–	0.5	–	–
Healthy diet score	–	–	–	–	2.9

Values are percentages unless indicated otherwise.
*Analytical cohorts obtained after exclusion of those with a history of abdominal aortic aneurysm or cancer, and those with missing data on primary exposures (apart from Study V, see Figure 4 for a detailed description of exclusions).

Assessment of interaction

Biological mechanisms are complicated enough that some causes of a certain disease can be expected to have an effect only under certain conditions. For example, if we accept that cigarette smoking is a causal factor in AAA development, and assume that 1 out of 20 heavy smoking men eventually develop AAA, there must be an interaction between some biological mechanism and the cigarette smoke which cause AAA only in those 5% of heavy smokers. Another example of interaction is that of drunk driving; both alcohol consumption and driving are risk factors for injury, but a combination of the two is much more potent than either of the two alone. Given that we are aware of causal interaction in almost all diseases, it is important to be aware of the concept of interaction in statistical modelling, and epidemiological interpretation.

In statistics, the term interaction refers to an inclusion of a product term between two predictors in a statistical model. Departure from the null hypothesis (that the product is not associated with the outcome) in a multiplicative model indicates the presence of a multiplicative interaction between those variables, and an additive interaction if the scale is additive. This is referred to as the Wald test, which is a parametric test that assumes that the standard error of the parameter is known, and that the distribution of the parameter is chi-squared.

Another way to assess statistical interaction is with the likelihood ratio test. This test has its advantages compared to the Wald test since it does not rely on awareness of the standard error of the parameter. Instead, the test compares goodness of fit of two separate models; one original model, and one with the product term. The likelihood ratio indicates how many times more likely the data are under one model compared with the other. This test can be used when deciding whether or not the original model can be rejected in favor of the one with the product term.

Effect modification is very similar to the idea of interaction, but rather refers to the situation in which the effect of an exposure on the outcome depends on the value of another covariate. To assess effect modification, one needs to stratify on the covariate of interest, and then, for example, calculate the likelihood ratio between those two models. By doing so, however, one misses the joint effect of the two exposures.

Possible interactions/effect modifications on AAA risk in this thesis were tested between the exposures of interest and sex (Study I-III), smoking status (Study II-IV), CVDs (Study I-V), hyperlipidemia (Study III), hypertension (Study V), and diabetes (Study V). The Wald test was used to assess statistical significance of the interaction term in Study II and V, while the likelihood ratio test was used in Study I, III, and IV.

Sensitivity- and sub analyses

Several sensitivity- and subanalyses were performed to try to sort out whether the observed results were biased. In Study I-IV, the outcome was assessed through AAA diagnosis and/or repair, and ultrasound examinations were not performed in all participants that were followed-up. Hence, there is a risk that some of the participants in the cohorts actually had an AAA, without their own awareness, but it had not been diagnosed yet. That is, there is most likely some degree of underdiagnosis of AAA, or in other words, the sensitivity of AAA is not 100%. If misclassification of the disease depended on some variable, it could have biased the observed results (further discussed in *Methodological considerations, Misclassification of cases*). For example, a smoking participant is at higher risk of developing cardiovascular diseases, and a patient with such disease may seek healthcare more often than a non-smoking one and, thus, it is more likely that an AAA is detected. In this case, the observed risk of AAA disease might not only be due to a biological association between smoking and AAA, but also be affected by the proneness of seeking healthcare.

To try to sort this issue out, we performed sensitivity analyses by restricting the outcome to repair of iAAA, and rAAA, indicating a diameter ≥55mm for men, and ≥50mm for women. As screening was introduced in 2006, we performed analyses by restricting the follow-up to 31 December 2005.

Furthermore, analyses were performed by restricting analyses to participants without baseline diagnosis of CVD, hypertension, diabetes, and hypercholesterolemia, and further by censoring follow-up at date of diagnosis for those participants who developed CVD, diabetes, and hypertension. Furthermore, as some of the comorbid diseases may be intermediary factors in AAA development, sensitivity analyses were also performed by excluding hypertension and diabetes as covariates in the models.

Further sensitivity analyses were performed by excluding the first three years of follow-up, as baseline exposure could have been secondary to preclinical or chronic illness (Study I-IV). In Study V, we also performed a sensitivity analysis by restricting the outcome to an AAD ≥35 mm to account for potential errors in ultrasound measurements.

Furthermore, sub-analyses were performed. For example, analyses were stratified by smoking status, and by specific fruits and vegetables, in Study III, and by specific alcoholic beverages in Study IV. To take into account a potentially decreased longevity and a reduced time at AAA risk among those who consumed low amounts of fruit and vegetables, a competing risk analysis was performed with all-cause mortality as competing risk in Study III.

RESULTS

Study I. Smoking

Participants were followed-up from 1 January 1998 to 31 December 2011. During the 14 years, 1157 participants were identified with AAA, of whom 958 (83%) were men. We observed 220 ruptures (178 in men [81%]). Median age at AAA diagnosis was 74 years among men, respectively 77 years among women.

Current smokers tended to be younger, and consume more alcohol and less fruit than those who did not smoke, and were less likely to be highly educated. Men who had ever smoked were more likely to have comorbid diseases (e.g. CVDs, hypertension, diabetes, and hypercholesterolemia).

The age-standardized 14-year incidence of AAA per 100,000 person-years was higher among men for all different levels of smoking. However, current smoking women had a higher AAA incidence than never smoking men, irrespective of how restricted the definition of AAA was (Table 4).

The absolute hazards of AAA were higher among men than women for each specific level of exposure to smoking. However, the relative risks of AAA associated with smoking seemed to be of a larger magnitude among women compared with men ($P_{interaction}$ with sex = 0.002). When comparing with never smokers, the hazard of AAA among current smokers who had smoked ≥20 pack-years, was increased 11-fold among women, respectively 7-fold among men. Among past smokers who had stopped smoking <20 years before baseline, the AAA hazard was 5-fold higher among women, and 4-fold higher among men, compared with never smokers. For those that had stopped smoking ≥20 years prior to baseline, the hazard among women did not differ compared with never smokers, while the ratio remained increased by 61% among men (Figure 6).

Table 4. Incidence of abdominal aortic aneurysm (AAA), by smoking status

Standardized incidence rate (per 100.000 person-years)*	Smoking status					
	Women			Men		
	Never	Past	Current	Never	Past	Current
All AAA events	17 (13 – 22)	46 (34 – 63)	136 (108 – 168)	76 (64 – 89)	206 (186 – 228)	365 (330 – 403)
Intact AAA	12 (9 – 17)	37 (25 – 51)	109 (85 – 138)	61 (51 – 73)	160 (143 – 179)	297 (266 – 331)
Large AAA †	9 (6 – 14)	28 (18 – 41)	58 (40 – 82)	33 (26 – 42)	105 (91 – 121)	196 (170 – 225)
Intact AAA repair	4 (2 – 8)	18 (10 – 29)	32 (20 – 49)	19 (13 – 25)	59 (48 – 71)	128 (108 – 151)
Ruptured AAA	5 (3 – 8)	10 (5 – 19)	27 (14 – 45)	15 (10 – 21)	46 (37 – 58)	68 (52 – 87)

Values in parentheses are 95% confidence intervals. AAA indicates abdominal aortic aneurysm.
*) Standardized according to the distribution of age in the Cohort of Swedish Men.
†) Ruptured AAA or AAA repair.

When continuously modeled with restricted cubic splines among ever smokers, the hazard of AAA increased for every 5 pack-year smoked by 13% (95% CI, 6% to 19%) among women, and by 11% (95% CI, 9% to 13%) among men. Among current smokers (Figure 7), there was evidence of a non-linear association between pack-years smoked and AAA hazard for both sexes ($P_{non-linearity} < 0.001$), and the AAA hazard increased up to, approximately, 30 pack-years smoked, after which the association seemed to reach a plateau. Among past smoking men, pack-years smoked demonstrated a non-linear relationship with AAA hazard ($P_{non-linearity} = 0.032$), where the hazard increased up to, approximately, 15 pack-years smoked, after which the association reached a plateau (Figure 7). Although the HR estimates were similar to those of men, pack-years smoked was not significantly associated with AAA risk among women ($P_{overall} = 0.22$), and there was no evidence of an interaction between sex and past ($P_{interaction} = 0.19$), or current ($P_{interaction} = 0.51$), smoking, regarding AAA hazard.
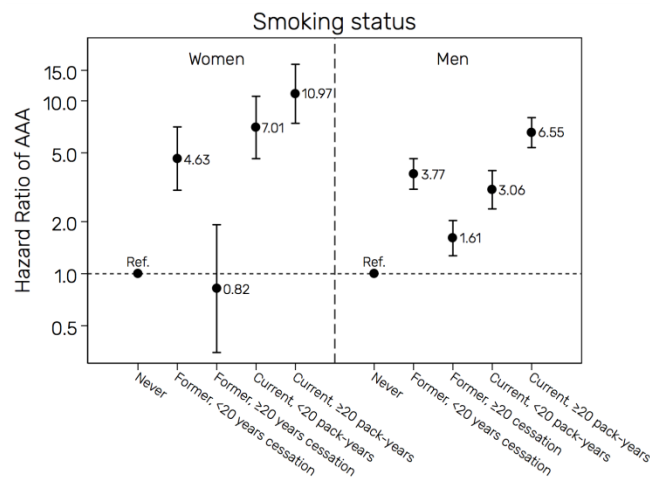

Figure 6. Multivariable adjusted hazard ratios of abdominal aortic aneurysm (AAA), by smoking status. Dots represent point estimates and bars represent 95% confidence intervals. Vertical axis is on a log scale.
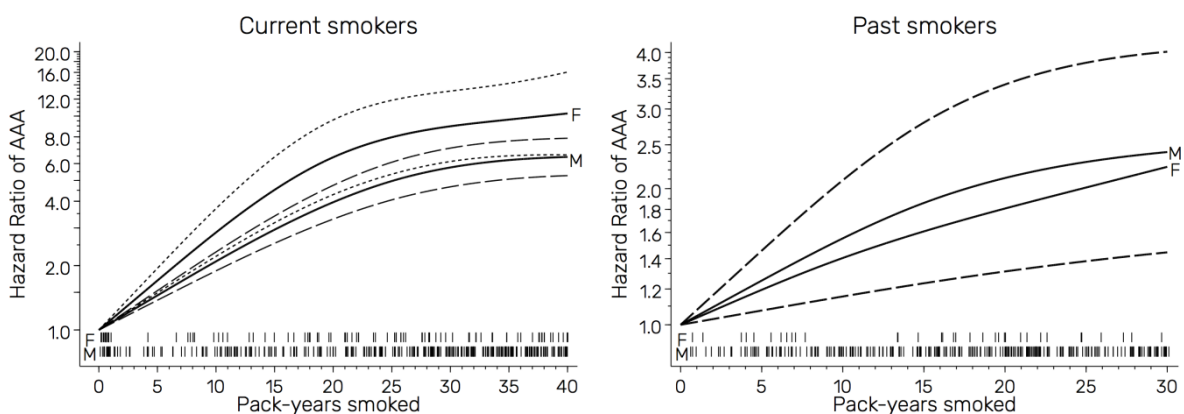

Figure 7. Multivariable adjusted hazard ratios for abdominal aortic aneurysm (AAA) associated with numbers of pack-years smoked among current- and past smoking men (solid M-line) and women (solid F-line). Data were fitted with a Cox proportional hazards regression model with restricted cubic splines with three knots at fixed percentiles (10th, 50th, and 90th) of the distribution of pack-years smoked. Dashed lines for men, and dotted lines for women, represent 95% confidence limits (pack-years smoked was not associated with AAA among past smoking women). Never smokers at null served as reference. Vertical axis is on a log scale. Tick marks represent the distribution AAA-events among men (M-row), and women (F-row).

When compared with current smoking, the AAA hazard decreased in a linear fashion ($P_{non-linearity}$ = 0.50, and 0.75, among women and men, respectively) with years since smoking cessation by 7% (95% CI, 5% to 9%) among women, and 3% (95% CI, 2% to 4%) among men (Figure 8). There was evidence of an interaction between sex and years since cessation regarding AAA hazard ($P_{interaction}$ < 0.001). Among women, the excess risk associated with continued smoking decreased to half the level after 11 years since cessation, while a corresponding decrease in excess risk was observed after 23 years among men.

When the outcome was restricted to AAA repair and rAAA, the HRs among current smokers with ≥20 pack-years smoked, compared with never smokers, were 8.45 (95% CI, 4.69 to 15.21) among women, respectively 7.85 (95% CI, 5.85 to 10.54) among men. Corresponding HRs of AAA when the follow-up was restricted to 31 December 2005 were 7.72 (95% CI, 4.36 to 13.66) among women, respectively 7.74 (95% CI, 5.46 to 10.96) among men. For the other categories of smoking status, and for the continuous analyses, interpretations of observed results did not differ when the outcome was restricted to AAA repair and rAAA, or when end of follow-up was set to 31 December 2005. The age-adjusted incidence of AAA per 100.000 person-years between baseline and 31 December 2005 among never, former, respectively current, smokers were 16 (95% CI, 11 to 23), 41 (95% CI, 26 to 62), and 94 (95% CI, 65 to 130), among women. Corresponding incidences among men were 37 (95% CI, 28 to 50), 131 (95% CI, 111 to 153), respectively 219 (95% CI, 185 to 258).

When models were restricted to participants without CVD at baseline, when censoring those who developed CVD or cancer during follow-up, or when the first three years of follow-up were excluded, results did not differ. No evidence of an interaction between CVD and smoking habits was observed.
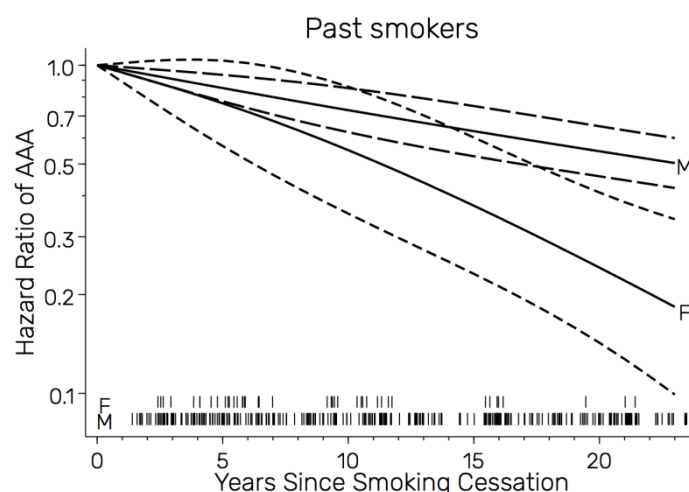

Figure 8. Multivariable adjusted hazard ratios for abdominal aortic aneurysm (AAA) associated with years since smoking cessation among current- and past smoking men (solid M-line) and women (solid F-line). Data were fitted with a Cox proportional hazards regression model with restricted cubic splines with three knots of the distribution of years since smoking cessation (0, 8, and 31 years for men, respectively 0, 5, and 29 years for women). Dashed lines represent 95% confidence limits. Current smokers at null served as reference. Vertical axis is on a log scale. Tick marks represent the distribution of AAA-events among men (M-row), and women (F-row), who had ceased to smoke at baseline.

Study II. Obesity

Participants were followed-up from 1 January 1998 to 31 December 2009. During the 12 years, 597 participants were identified with iAAA, of whom 492 (82%) were men. The mean age at diagnosis was 74 years among men, respectively 76 years among women.

Participants with an increased waist circumference and high BMI were more likely to have a history of comorbid disease, and less likely to have a higher educational level. Those with larger waist circumferences tended to consume more alcohol than those with a normal waist circumference.

The iAAA hazard increased with increasing waist circumference. Compared with those with a normal waist circumference, the hazard of iAAA was increased by 30% (95% CI, 5% to 60%) among those with an increased waist circumference (Figure 9). When waist circumference was modeled flexibly with restricted cubic splines, iAAA hazard increased by 15% (95% CI, 5% to 26%) per 5 cm increment until a level of 100 cm for men (HR 1.14; 95% CI, 1.03 to 1.26), and 88 cm for women (HR 1.16; 95% CI, 0.95 to 1.42), after which the HRs of iAAA seemed to reach a plateau (Figure 10). The prevalence of diabetes at baseline below, respectively above, these observed threshold values in waist circumference was 10.1%, respectively 4.9%. This study only utilized iAAA as outcome. However, if rAAA was included (as in Study I, III, and IV), results were similar; the HR among those with an increased, respectively a substantially increased, waist circumference was increased by 25% (95% CI, 3% to 51%), respectively 26% (95% CI, 0% to 58%), when comparing with those with a normal waist circumference.

The positive association between waist circumference and iAAA remained when analyses were restricted to individuals without baseline history of CVD, hypertension, hypercholesterolemia, or diabetes, when participants who developed CVD during follow-up were censored at date of diagnosis, when not adjusting for comorbid disease, when excluding the first three years of follow-up, and when follow-up was restricted to 31 December 2005. There was no evidence of an interaction between waist circumference and sex ($P_{interaction}$ = 0.34), smoking status ($P_{interaction}$ = 0.13), hypercholesterolemia ($P_{interaction}$ = 0.33), or CVD ($P_{interaction}$ = 0.79), regarding iAAA hazard.

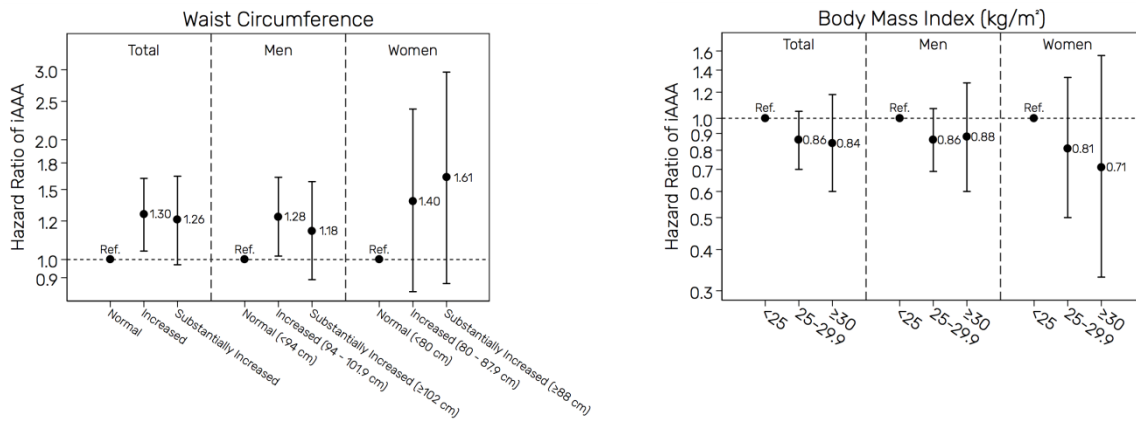There was no observed association between BMI and AAA hazard when adjusting for waist circumference (Figure 9).

Figure 9. Multivariable adjusted hazard ratios of intact abdominal aortic aneurysm (iAAA), by categories of waist circumference and Body Mass Index. Dots represent point estimates and bars represent 95% confidence intervals. Vertical axis is on a log scale.

Figure 10. Multivariable adjusted hazard ratios of intact abdominal aortic aneurysm (iAAA) associated with waist circumference among men and women. Data were fitted with a Cox proportional hazards regression model with restricted cubic splines with three knots of the distribution of waist circumference (85, 95, and 108 cm for men, respectively 72, 82, and 96 cm for women). Dashed lines represent 95% confidence limits. The value of 100 cm, and 88 cm, served as reference value among men, and women, respectively. The vertical axis is on a log scale. Tick marks represent the distribution of iAAA events. The histogram is the distribution of waist circumference in the two cohorts.

Study III. Fruit and vegetable consumption

Participants were followed-up from 1 January 1998 to 31 December 2010. During the 13 years, 1086 participants were identified with AAA, of whom 899 (83%) were men. We observed 222 ruptures (181 in men [82%]). The mean age at diagnosis of iAAA, respectively rAAA, was 74, and 76, years among men, respectively 76, and 79, years among women.

Participants with a high consumption of fruit and vegetables were more likely to be highly educated, leaner, physically active, to consume more fish, meat and whole grains, and less likely to smoke. Less alcohol was consumed among high consumers of fruits, while more alcohol was consumed among high consumers of vegetables.

AAA hazard decreased with increasing consumption of fruit. In the total population, the hazard of AAA was 25% (95% CI, 9% to 38%) lower among participants in the highest quartile of fruit consumption (>2.0 servings/day), compared with those in the lowest quartile (<0.7 servings/day) (Figure 11). Corresponding hazard of iAAA was 19% (95% CI, -1% to 35%) lower, while the hazard of rAAA was 43% (95% CI, 11% to 64%) lower, in the highest compared with the lowest quartile of fruit consumption. Estimates were similar among men and women. In subanalyses of specific fruits and vegetables, none of the single items were significantly associated with AAA risk.

When flexibly modeled with restricted cubic splines, the hazard of iAAA seemed to decrease with fruit consumption up to approximately two daily servings of fruit, after which the association levelled out ($P_{non-linearity}$ = 0.004) (Figure 12). The hazard of rAAA was observed to decrease in a linear fashion ($P_{non-linearity}$ = 0.36) by 17% (95% CI, 3% to 30%) for each additional daily serving of fruit (Figure 12). One, two, and three daily servings of fruit, compared with no consumption, was associated with a statistically significant decrease in iAAA hazard by 24%, 31%, and 27%, respectively. Corresponding hazards of rAAA were decreased by 27%, 39%, and 44%, respectively.

There was no formal evidence of an interaction between fruit consumption and sex, smoking status, or CVD, regarding AAA hazard. However, in stratified analyses by smoking status, fruit consumption was not associated with rAAA among never smokers (HR, 1.02; 95% CI, 0.39 to 2.70), while the hazard of rAAA comparing the highest with the lowest quartile of fruit consumption was decreased by 58% (95% CI, 6% to 81%) among past smokers, respectively 61% (95% CI, 6% to 83%) among current smokers. Results did not change substantially when analyses were restricted to participants without baseline history of CVD, when participants who developed CVD during follow-up were censored at date of diagnosis, when the first three years of follow-up were excluded, when follow-up was restricted to 31 December 2005, or in a competing risk model with all-cause mortality as the competing risk.

Vegetable consumption was not associated with hazard of AAA, iAAA, or rAAA.

Figure 11. Multivariable adjusted hazard ratios of abdominal aortic aneurysm (AAA), by quartiles of fruit (<0.7, 0.7-1.2, 1.3-2.0, respectively >2.0 daily servings), and vegetable (<1.4, 1.4-2.2, 2.2-3.3, respectively >3.3 daily servings), consumption. Dots represent point estimates and bars represent 95% confidence intervals. Vertical axis is on a log scale.

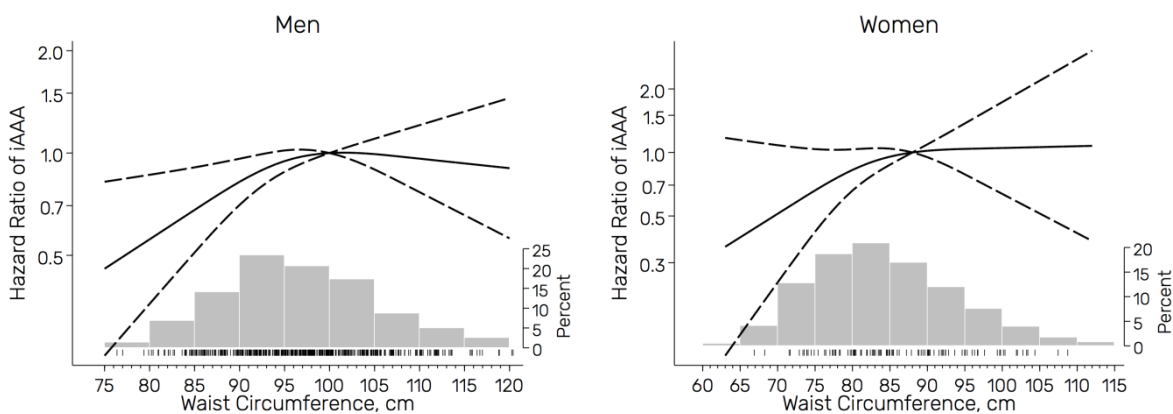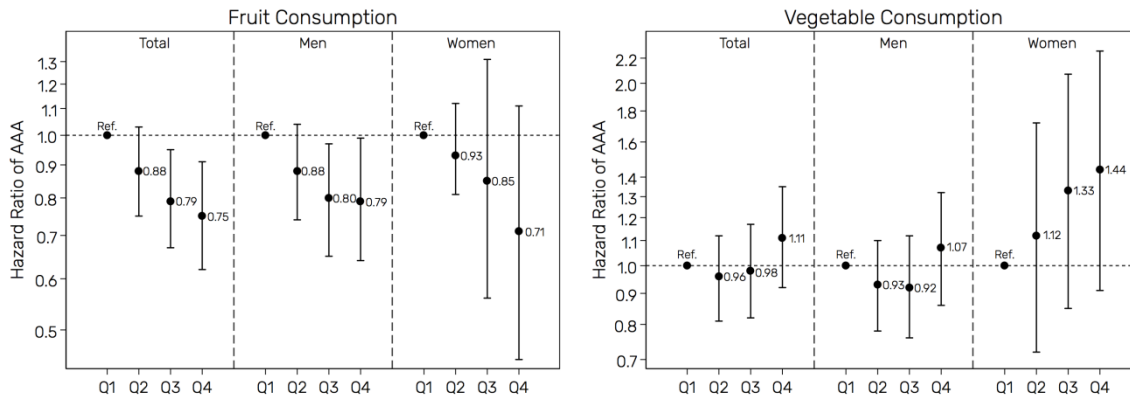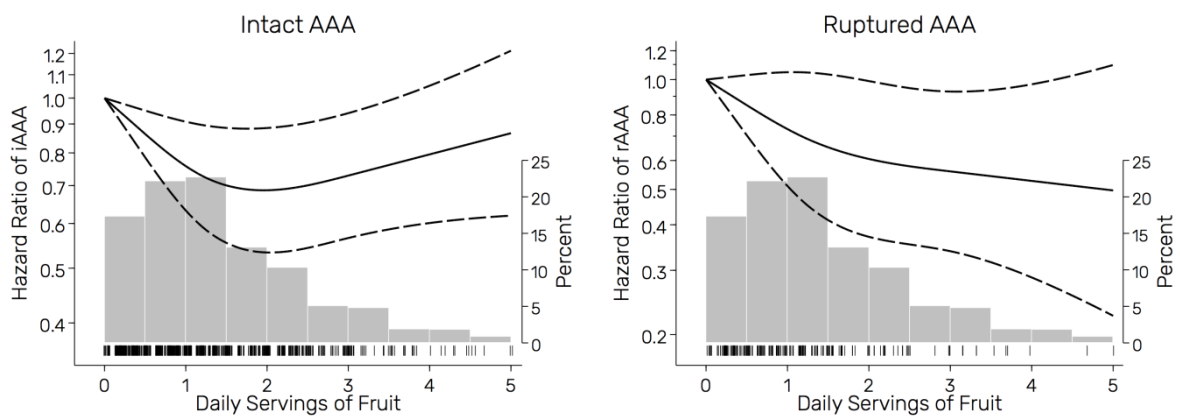**Figure 12.** Multivariable adjusted hazard ratios of intact abdominal aortic aneurysm (iAAA), and ruptured abdominal aortic aneurysm (rAAA), associated with fruit consumption among men and women. Data were fitted with a Cox proportional hazards regression model with restricted cubic splines with three knots of the distribution of fruit consumption (0.4, 1.2, and 3.0 servings/day). Dashed lines represent 95% confidence limits. Zero daily servings served as reference. The vertical axis is on a log scale. Tick marks represent the distribution of iAAA, respectively rAAA, events.The histogram is the distribution of fruit consumption in the two cohorts.

Study IV. Alcohol consumption

Participants were followed-up from 1 January 1998 to 31 December 2011. During the 14 years, 1214 participants were identified with AAA, of whom 1020 (84%) were men. We observed 238 ruptures (195 in men [82%]). Mean age at AAA diagnosis was 74, respectively 76, years among men and women.

Participants with a high consumption of alcohol tended to be younger, more likely to be current smokers, have a higher degree of education, and less likely to have diabetes or CVDs, compared with those with a low consumption. Men with a high consumption were more likely to have hypertension, hypercholesterolemia, and a larger waist circumference, while the inverse applied among women. Former drinkers were more likely to be smokers, have comorbid conditions, and less likely to have a university education. The mean proportions of different alcoholic beverages that constituted the total consumption of alcohol among current drinking men were 50% beer, 26% wine, and 24% spirits. Corresponding proportions among current drinking women were 34% beer, 54% wine, and 12% spirits.

An inverse association with total alcohol consumption among both men and women was observed. Compared with men who consumed <2 glasses of alcohol/week, the AAA hazard among men who consumed 4–6 glasses/week was 20% lower. Corresponding hazard among women was 44% lower, when comparing with women who consumed <1 glasses/week.

When flexibly modeled with restricted cubic splines, the AAA hazard decreased with increasing consumption of alcohol up to approximately 10 glasses/week among men, respectively 5 glasses/week among women, after which the association seemed to level out ($P_{\text{non-linearity}}$ = 0.030 for men, and 0.001 for women) (Figure 13). Compared with a consumption of 1 glass/week, 10 glasses/week was associated with a 20% (95% CI, 6% to 32%) decrease in AAA hazard among men, whereas the corresponding decrease was 43% (95% CI, 18% to 60%) among women who consumed 5 glasses/week. HRs did not change when also including never and former drinkers at zero consumption. Consumption of beer and wine was associated with a decreased AAA hazard but only the associations with beer in men, and wine in women, were statistically significant. Consumption of spirits did not seem to be associated in either men or women (Figure 14). In stratified analyses, the HRs did not differ by age group ($P_{\text{interaction}}$ = 0.60 for men, and 0.32 for women), CVD ($P_{\text{interaction}}$ = 0.46 for men, and 0.12 for women) or smoking status ($P_{\text{interaction}}$ = 0.88 for men, and 0.37 for women) at baseline.

When participants with CVD at baseline were excluded, and the follow-up time was censored for those who developed CVD during the study course, the observed inverse associations for total alcohol consumption were not statistically significant (Figure 15). However, consumption of beer among men, and wine among women, was still significantly associated with lower AAA hazards (Figure 16).

Observed results did not differ when the outcome was restricted to rAAA and AAA repair, or when the end of follow-up was restricted to 31 December 2005.

Figure 13. Multivariable adjusted hazard ratios of abdominal aortic aneurysm (AAA) associated with alcohol consumption among current drinking men and women. Data were fitted with a Cox proportional hazards regression model with restricted cubic splines with three knots of the distribution of alcohol consumption (1, 6, and 18.4 glasses/week for men, respectively 0.4, 2.6, and 8.6 glasses/week for women). Dashed lines represent 95% confidence limits. One glass (12g of ethanol) per week served as reference. The vertical axis is on a log scale. Tick marks represent the distribution of iAAA events.The histogram is the distribution of alcohol consumption in the two cohorts. The lower x-axis transcripts glasses/week into grams/day.

Figure 14. Multivariable adjusted hazard ratios of abdominal aortic aneurysm (AAA), by specific alcoholic beverages among current drinking men and women. Dots represent point estimates and bars represent 95% confidence intervals. Vertical axis is on a log scale.
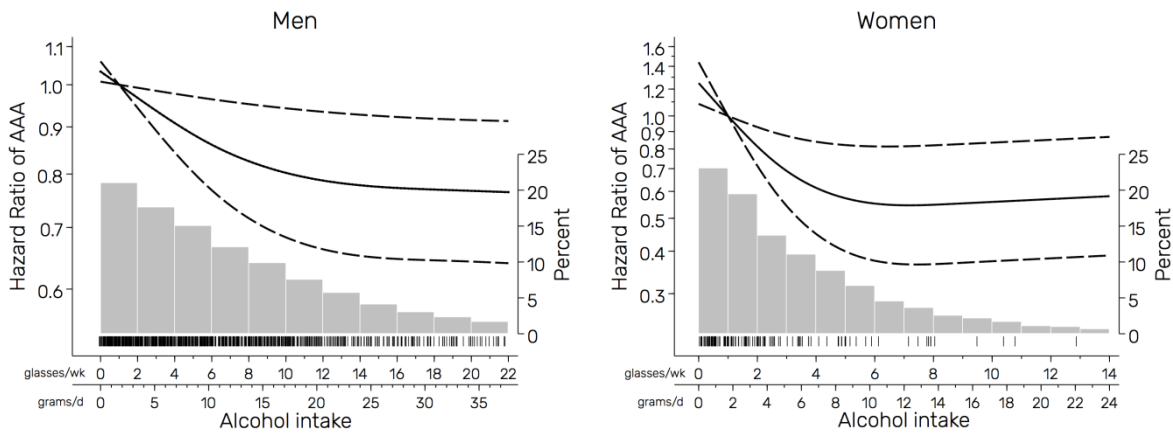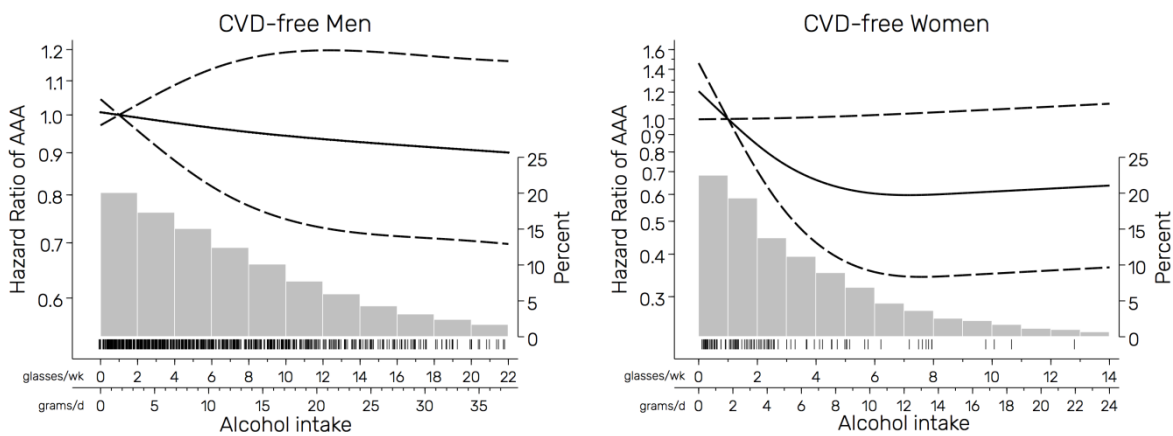
Figure 15. Multivariable adjusted hazard ratios of abdominal aortic aneurysm (AAA) associated with alcohol consumption among current drinking men and women without cardiovascular disease (CVD) at baseline, and censored at date of CVD-diagnosis during follow-up. Data were fitted with a Cox proportional hazards regression model with restricted cubic splines with three knots of the distribution of alcohol consumption (1, 6.2, and 18.6 glasses/week for men, respectively 0.4, 2.6, and 8.8 glasses/week for women). Dashed lines represent 95% confidence limits. One glass (12g of ethanol) per week served as reference. The vertical axis is on a log scale. Tick marks represent the distribution of iAAA events. The histogram is the distribution of alcohol consumption in the two cohorts. The lower x-axis transcripts glasses/week into grams/day.
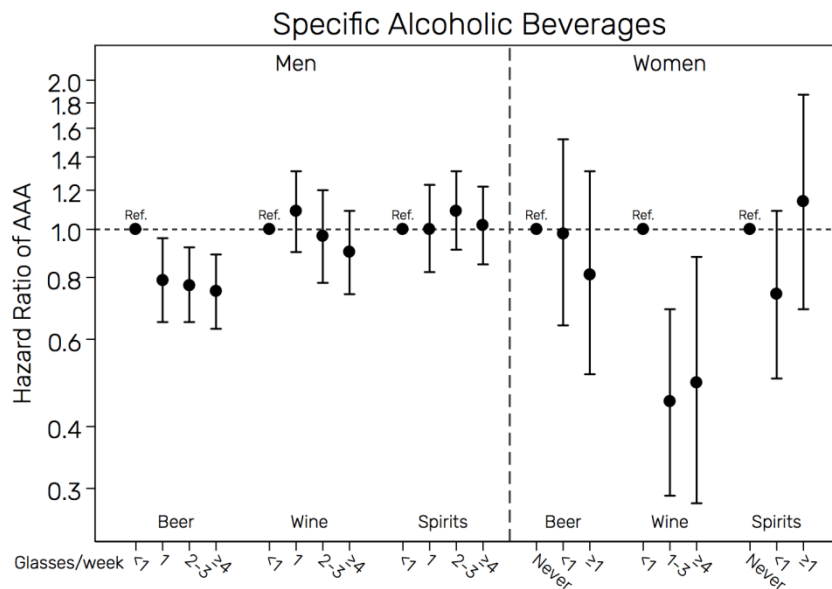

Figure 16. Multivariable adjusted hazard ratios of abdominal aortic aneurysm (AAA), by specific alcoholic beverages among current drinking men and women without cardiovascular disease (CVD) at baseline, and censored at date of CVD-diagnosis during follow-up. Dots represent point estimates and bars represent 95% confidence intervals. Vertical axis is on a log scale.

Study V. Lifestyle and aortic diameter
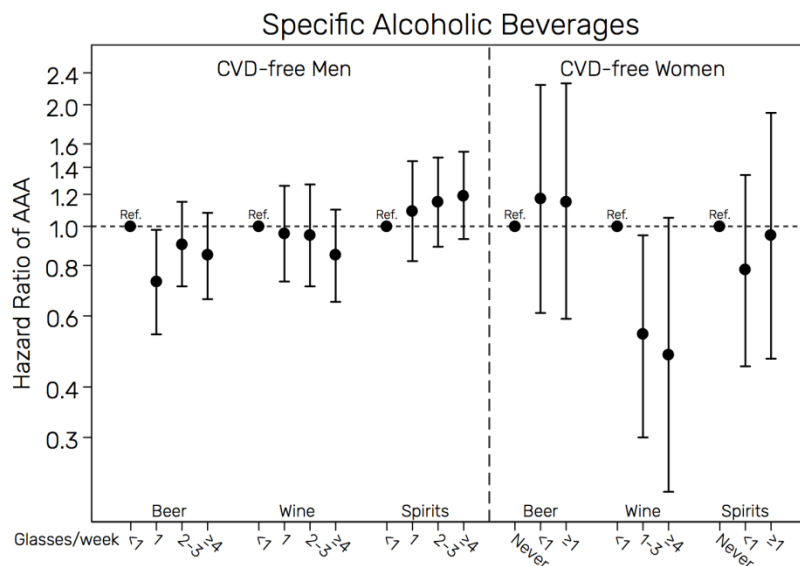
We identified 14,249 men in the COSM that had undergone screening for AAA between 65 and 75 years of age (mean follow-up to screening 13 years). An AAA was detected in 168 (1.2%) men. Mean age at baseline was 55 years, and mean age at screening was 68 years.

Compared with those with an AAD <30mm, participants with AAA disease seemed to have a lower consumption of healthy foods, be less likely to have a university educational degree, and being physically active, and more likely to have a larger waist circumference and higher BMI, be current smokers, and to have comorbid diseases.

In a linear prediction model with AAD as dependent variable, current smoking, pack-years smoked, CVDs, and BMI, were associated with an increased diameter (Figure 17). Every 5 pack-years smoked was associated with a 0.21 mm (95% CI, 0.16 mm to 0.26 mm) increase in mean AAD ($P_{non-linearity}$ = 0.061), while each increment in BMI-unit was associated with a mean increase of 0.11 mm (95% CI, 0.06 mm to 0.16 mm) ($P_{non-linearity}$ = 0.21) (Figure 18).

The hazard of AAA (AAD $\geq$30 mm) was increased among those who were former or current smokers, had higher levels of BMI, and among those with hypercholesterolemia or CVDs. Those who walked/bicycled >40 min/day had a 41% lower hazard of AAA as compared with those who almost never were walked/bicycled (Figure 19).

When modeled continuously with restricted cubic splines (Figure 20), there was evidence of a non-linear association between AAA hazard and pack-years smoked ($P_{non.linearity}$ = 0.003), but not BMI ($P_{non-linearity}$ = 0.92). For every 5 pack-years smoked, the AAA hazard increased by 50% (95% CI, 22% to 85%) up to approximately 20 pack-years smoked, after which the association reached a plateau. Each increment in BMI-unit was associated with a 9% increase in AAA hazard (95% CI, 2% to 17%).

There was no evidence of an interaction between lifestyle-related exposures and CVD, hypertension, or diabetes, regarding AAA hazard or AAD. Exclusion of those with hypertension and/or diabetes at baseline and censoring of follow-up time at date of diagnosis for participants who developed those diseases during follow-up did neither change the results.

To account for potential ultrasound measurement errors, an AAD $\geq$35mm was also investigated as outcome (n=91). The HR of an AAD $\geq$35mm was 14.41 (95% CI, 6.58 to 31.57) for current smokers with $\geq$25 pack-years smoked vs never smokers, 2.18 (95% CI, 1.20 to 3.97) for a BMI $\geq$25 kg/m2 vs a BMI <25, 0.71 (95% CI, 0.36 to 1.42) for $\geq$40 minutes of walking/bicycling vs almost never, 0.55 (95% CI, 0.31 to 1.00) among those with a healthy diet score >12 vs <9, 0.73 (95% CI, 0.47 to 1.13) among those consuming $\geq$1 glass of alcohol/day vs those who consumed <1 glass/day, 2.11 (95% CI, 1.18 to 3.78) for CVD, respectively 1.88 (95% CI, 1.12 to 3.15) for hypercholesterolemia.
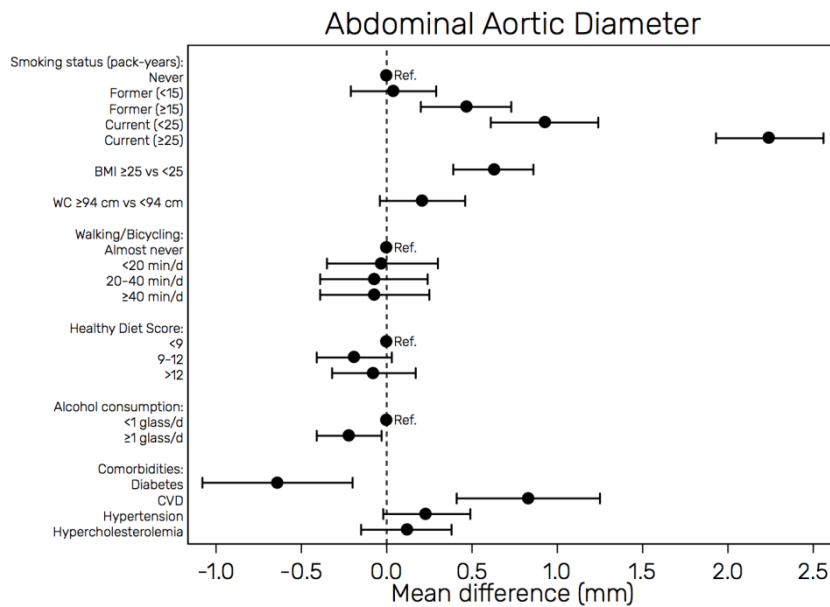
Figure 17. Multivariable predicted mean difference in abdominal aortic diameter, by lifestyle exposures and comorbidities, among men screened for AAA between 65 and 75 years of age. Dots represent point estimates and bars represent 95% confidence intervals. Horizontal axis is on a numeric scale. CVD indicates cardiovascular disease; WC, waist circumference.

Figure 18. Multivariable predicted mean difference in abdominal aortic diameter (AAD), by pack-years smoked and Body Mass Index (BMI), among men screened for AAA between 65 and 75 years of age. Data were fitted with a Cox proportional hazards regression model with restricted cubic splines with three knots of the distribution of pack-years smoked (0, 7.4, and 34.3 pack-years), and BMI (22.2, 25.6, and 30 kg/m^2). Dashed lines represent 95% confidence limits. Vertical axis is on a numeric scale. Tick marks represent the distribution of AAA cases according to pack-years smoked and BMI. Histograms represent the percentage distribution of pack-years smoked among ever smokers, respectively BMI.
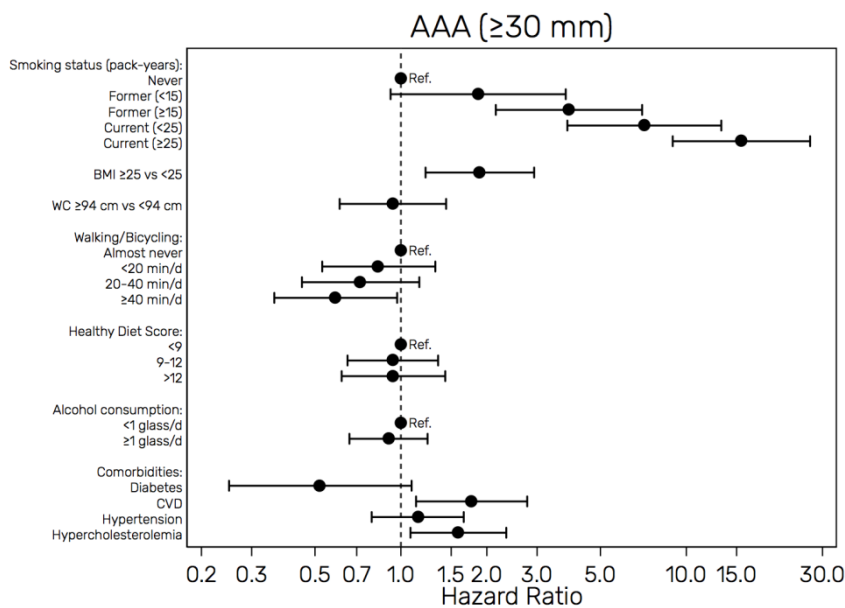
Figure 19. Multivariable adjusted hazard ratios of abdominal aortic aneurysm (AAA), by lifestyle exposures and comorbidities, among men screened for AAA between 65 and 75 years of age. Dots represent point estimates and bars represent 95% confidence intervals. Horizontal axis is on a log scale. CVD indicates cardiovascular disease; WC, waist circumference.
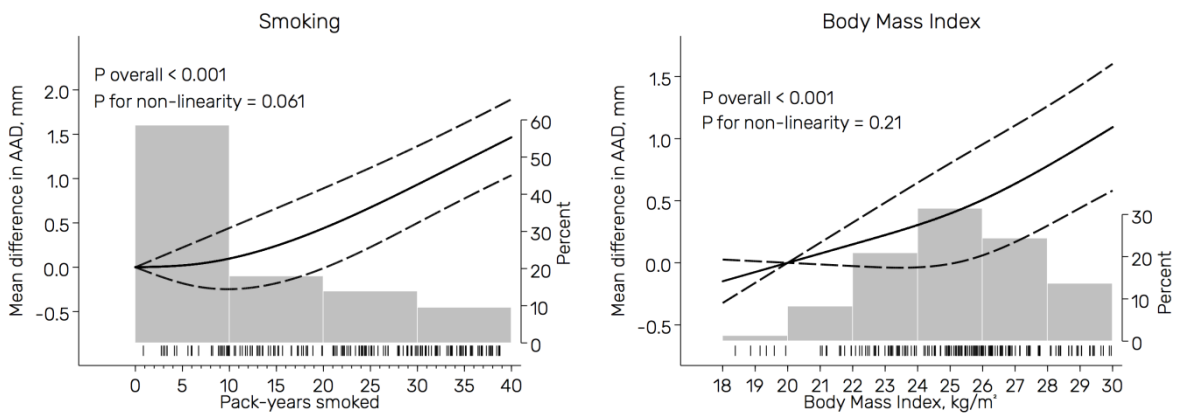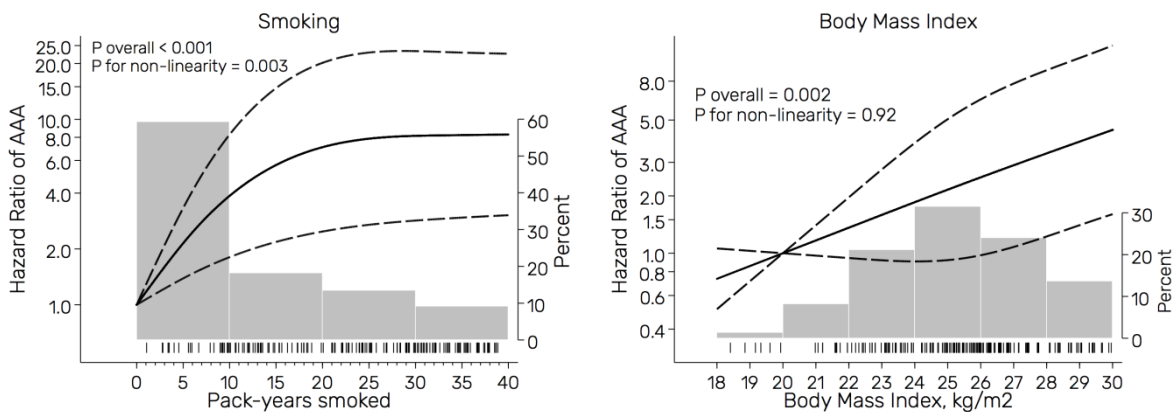

Figure 20. Multivariable adjusted hazard ratios of abdominal aortic aneurysm (AAA), by pack-years smoked, and Body Mass Index (BMI), among men screened for AAA between 65 and 75 years of age. Data were fitted with a Cox proportional hazards regression model with restricted cubic splines with three knots of the distribution of pack-years smoked (0, 7.4, and 34.3 pack-years), and BMI (22.2, 25.6, and 30 kg/m^2). Never smokers with zero pack-years smoked, respectively a BMI of 20, served as reference. Dashed lines represent 95% confidence limits. Vertical axis is on a log scale. Tick marks represent the distribution of AAA cases according to pack-years smoked , and BMI. Histograms represent the percentage distribution of pack-years among ever smokers, respectively BMI.

DISCUSSION

Main findings and general discussion

Main findings

The results in this thesis support that modifiable lifestyle-related factors are associated with risk of abdominal aortic aneurysm (AAA). The associations between smoking status, and smoking cessation, and risk of AAA differed between men and women. Generally, men are included in AAA screening programs, regardless of smoking status, while women who smoke are you usually not. However, we observed that smoking women had a higher AAA incidence than never smoking men. The absolute risks of AAA were higher among men for all specific smoking strata, but the relative risks associated with smoking seemed to be of larger significance for women, an observation that could not be explained by numbers of pack-years smoked. Smoking cessation halved the excess risk associated with current smoking twice as fast among women.

We also observed that obesity was associated with an increased risk of AAA. Waist circumference was associated with risk of iAAA diagnosis and/or repair among both men and women, while BMI was associated with risk of AAA and a larger mean AAD among men screened for AAA between 65 and 75 years of age. Increased physical activity was associated with a decreased risk of AAA detected at screening. Consumption of fruit, but not vegetables, was inversely associated with risk of AAA diagnosis and/or repair. The association was more pronounced for rAAA than iAAA. Among men, a healthy diet in general did, however, not seem to be associated with AAA detected at screening, or with AAD.

Among men, diabetes and a moderate consumption of alcohol were associated with a smaller mean AAD. Moderate consumption of alcohol was also associated with a lower hazard of AAA diagnosis and/or repair among men and women in the whole study population, but did not seem to be associated in a subcohort of participants free from CVDs, or with AAA detected at screening. The most commonly consumed alcoholic beverages, i.e., beer among men and wine among women, were inversely associated with AAA diagnosis and/or repair in the entire population as well as in the CVD-free subcohort.

These findings contribute to a better understanding of AAA etiology and in a future, if confirmed by other studies, to evidence-based strategies for primary prevention of the disease. Furthermore, it is likely that patients diagnosed with AAA would benefit from lifestyle modification. For example, smoking, obesity, and comorbidity, have been associated with a higher degree of peri- and postoperative complications during AAA-repair (Barakat et al, 2014; Giles et al, 2010). A moderate consumption of alcohol, a healthy diet, and physical activity, have been associated with a decreased risk of other CVDs, which also increases the risk of the most common non-technical complications after AAA repair (Mitchell et al, 1995). Thus, even if a healthy lifestyle does not per se decrease aneurysm growth in small AAAs, patients are likely to do better when their AAA eventually need to be repaired if they have a healthy lifestyle.

General discussion

Smoking

We investigated the sex-specific associations between smoking status, and smoking cessation, and hazard of AAA diagnosis and/or repair. Female smokers are generally not included in AAA screening programs, however, we observed that this group had a significantly higher incidence of AAA than men who had never smoked, but usually are included in such programs. Regarding AAA hazard, current smoking seemed to affect women to a larger extent than men, an association not explained by numbers of pack-years smoked. After cessation, the excess risk associated with current smoking decreased to half the level twice as fast among women. Furthermore, among male heavy smokers (≥25 pack-years smoked), we observed a more than 15-fold higher risk of having an AAA at screening between 65 and 75 years of age, and that male smokers had a larger mean AAD, compared with men who had never smoked.

Comparable to these results, the odds of AAA was observed to increase by 11% per 5 pack-year smoked among women in the Women's Health Initiative Study (Lederle et al, 2008), while we observed a 13% increase in AAA hazard among women. Furthermore, Wilmink et al observed a 4% decrease in excess risk of AAA following each year since smoking cessation among men (Wilmink et al, 1999a), while the corresponding decrease was 3% among men in the COSM. In the Tromsø Study (Forsdahl et al, 2009), one of the only other investigations with a similar design as Study V of this thesis, the OR of incident AAA among current smokers with ≥20 cigarettes/day was increased 14-fold compared with never smokers, which is similar to the 16-fold increase in HR of AAA we observed among current smoking men with ≥25 pack-years smoked, when comparing with never smokers.

Due to the low prevalence, AAA screening among all women is not considered economically or clinically viable (Scott et al, 2002; Svensjo et al, 2013). There is a lack of data, however, regarding the possible feasibility of targeted screening of subpopulations (Lo et al, 2016). The prevalence of AAA has previously been observed to be similar in female smokers as in male non-smokers (Lederle et al, 1997a), while we observed that the AAA incidence among women who smoke may be almost twice as high as that among non-smoking men. In a Swedish screening study among 70-year old women, 95% of detected AAAs were in ever smokers, and the prevalence among smokers was 2.1% (Svensjo et al, 2013). Results from a Markov model has shown that screening would remain cost-effective down to a AAA prevalence of 0.35% (Glover et al, 2014). Regardless of risk factors, however, the U.S. Preventive Task Force's recommendations for AAA screening do not include women (Guirguis-Blake et al, 2014). In contrast, the American Society of Vascular Surgery recommends targeted screening of women with a history of smoking (ever smokers) or with a family history of AAA (Chaikof et al, 2009), while the Medicare Part B covers screening for women with family history of AAA (Moore, 2007). In Sweden, there is no consensus whether subgroups of women should be included for targeted screening or not. For example, no women are invited in Uppsala and Örebro County, while women with a history of smoking, CVD, family history of AAA, or hypertension, are invited to AAA screening in Västmanland County.

Obesity

We investigated whether central obesity (as assessed with waist circumference) and/or total obesity (as assessed with BMI) were associated with hazard of iAAA diagnosis and/or repair, and with maximal infrarenal AAD. We observed a 30% increase in hazard of iAAA diagnosis and/or repair among those with an increased, compared with those with a normal, waist circumference. Every 5 cm increment was associated with a 15% increased risk of iAAA until the level of 100 cm for men, and 88 cm for women. There were no differences in the rate of change of the HR of iAAA between men and women. Above 100 cm for men and 88 cm for women, the iAAA hazard leveled off and did not increase further. This threshold is closely in agreement with the WHO classification of obesity status related to risk of CVD (substantially increased risk of CVD at a waist circumference of ≥102 cm for men and ≥88 cm for women) (WHO, 2000). Results did not change when also including rAAA as outcome. Among men screened for AAA between 65 and 75 years of age, an increased BMI, but not waist circumference, was associated with an increased risk of having an AAA, and with a larger mean AAD.

A more general inflammatory response due to total obesity may be of more importance in triggering AAA disease, while a more localized inflammatory response associated with a predominant localization of central obesity, may be of more importance to promote growth of an already diseased aorta (Barandier et al, 2005; Chatterjee et al, 2009; Eringa et al, 2007). It is possible that a clinical diagnosis and/or repair of AAA reflect AAA in its later stages, as opposed to the exact limit of 30 mm when defining AAA through ultrasound measured aortic diameter. Thus, factors that initiate dilatation might be different from those which promote AAA growth. Waist circumference is an approximate index of intra-abdominal fat mass, corresponding well to visceral adiposity (Pouliot et al, 1994; Ross et al, 1992), which correlates to abdominal periaortic adipose tissue (Schlett et al, 2009). Perivascular adipose tissue promotes inflammatory activity by releasing cytokines and adipokines (Barandier et al, 2005; Chatterjee et al, 2009; Eringa et al, 2007). AAA formation in mice has been found to increase through microphages infiltrating perivascular adipose tissue and through an increased expression of inflammatory cytokines (Police et al, 2009). The maximal diameter of an AAA has also been observed to decrease after weight loss in mice, which seemed to limit the progression of the disease (Police et al, 2010).

There was limited statistical power to investigate whether BMI or waist circumference were associated with larger diameters for which treatment would be recommended (only 16 men had an AAD ≥55mm at the time of screening). In an ad-hoc linear regression analysis restricted to participants screened with a sub-aneurysmal aorta or larger (≥25 mm, n=415), neither BMI nor waist circumference were associated with AAD.

The findings are comparable with other studies that included both measures of central and total obesity in the statistical models. For example, Golledge et al reported that the odds of AAA (defined as an AAD ≥30 mm) increased by 14% for every 10 cm increase in waist circumference (Golledge et al, 2007), and in the Veterans Affairs ADAM study, the odds of large AAAs (aortic diameter of ≥40 mm) increased by 15% for every 11 cm increase in waist circumference (Lederle et al, 1997a). None of these studies modeled waist circumference flexibly to investigate a possible non-linear relationship. When we forced the association to be linear, a 17% increase in hazard of iAAA diagnosis and/or repair for every 10 cm increase in waist circumference was observed. Given that the risk of diabetes also increases with increasing measures of obesity, and that diabetes has been reported to be inversely associated with risk of AAA (Lederle, 2012), the observed plateau observed with risk of AAA diagnosis and/or repair might be explained by an increased prevalence of diabetes among participants above the observed threshold. Among those below and above the observed threshold values, 4.9%, respectively 10.1%, had diabetes at baseline. In a large screening study of 65-year-old men from Central Sweden, there were no differences in prevalence of diabetes among those with and without AAA (Svensjo et al, 2011), which might be explained by counteracting effects of diabetes and obesity on AAA risk.

Diet

We observed that a high consumption of fruits, but not vegetables, was inversely associated with AAA diagnosis and/or repair. The reduction in hazard was more pronounced for rAAA than iAAA. We also observed that a healthy diet in general (as defined by consumption of fruits, vegetables, legumes, nuts, low-fat dairy products, whole grains, and fish) not was associated with hazard of AAA detected at screening, or with mean AAD, among men.

Related to the discussion of separate factors affecting AAA formation, as opposed to AAA growth, the same theory could be applied as an explanation for why a healthy diet was not associated with AAA detected at screening. Previous studies have observed cross-sectional, and prospective, associations between dietary habits and AAA. For example, Kent et al observed a 9% decrease in odds of AAA among individuals consuming a combined amount of fruits and vegetables >3 times/wk (Kent et al, 2010). Consumption of nuts was also inversely associated with AAA prevalence in that study, while an increased consumption of meat was associated with a higher AAA prevalence (Kent et al, 2010).

There was limited statistical power to investigate the associations between a healthy diet and hazard of larger diameters. In a linear regression analysis that was restricted to participants screened with a sub-aneurysmal aorta or larger (AAD ≥25 mm), every 5 increment in healthy diet score was associated with a smaller mean AAD. Furthermore, the HR of an AAD ≥35 mm was decreased by 45% (P=0.050) among those with a healthy diet score of >12 compared with those who had a score of <9. Although in support of the theory, which also is supported by the association of increased fruit consumption being more pronounced for rAAA, these analyses should be interpreted with caution given the low number of cases. However, it is also possible that only certain foods are capable of attenuating aortic wall inflammation, and that a healthy dietary pattern in general has little to no effect on AAA development, as previously suggested by Jamrozik et al (Jamrozik et al, 2001).

Bioactive phytochemicals in fruits and vegetables are likely to have many effects on vascular disease, but one possible explanation to the observed association with fruit consumption may be through a reduction of oxidative stress. Oxidative stress is an imbalance in the production and reduction of reactive oxygen species (ROS), and reactive nitrogen species (RNS), that has been observed to promote inflammation (Shah, 1997; Tegler et al, 2012). ROS and RNS have been found increased in human AAA tissue (Miller et al, 2002), and suggested to contribute to its formation through smooth muscle cell apoptosis (Henderson et al, 1999; Li et al, 2001; Li et al, 2003), matrix degradation (Rajagopalan et al, 1996), and recruitment of cytokines and other pro-inflammatory cells (Kaplan et al, 1999; Marumo et al, 1997).

Both fruit and vegetables are rich in antioxidants that could reduce oxidative stress and, thus, potentially reduce the risk of AAA (McCormick et al, 2007a). The null association between vegetable consumption and AAA hazard was, therefore, somewhat unexpected. However, none to small inverse associations with vegetable consumption has frequently been observed also for other CVDs, while fruit almost consistently seem to be inversely associated with such diseases (Dauchet et al, 2005; He et al, 2006; Hung et al, 2004; Hung et al, 2003).

Furthermore, fruits, but not vegetables, are rich in flavonoids (e.g. procyanidins) (Gu et al, 2004; Rasmussen et al, 2005). Procyanidins have been observed to inhibit the ROS-generating activity of the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in human endothelial cells of *in vitro* and *ex vivo* models (Alvarez et al, 2012b). The NADPH oxidase has, in turn, been suggested to play a role in the pathogenesis of AAA in animal models (Yajima et al, 2002a) and possibly also in humans by inhibiting oxidative stress in the aortic wall (McCormick et al, 2007b; Miller et al, 2002; Yajima et al, 2002b), and as a potential target for AAA treatment (McCormick et al, 2007a).

Even though there was no formal evidence of an interaction between fruit consumption and smoking status, there was an indication of a more pronounced association between fruit consumption and rAAA among ever smokers, while a null association was observed among never smokers. Since smoking increases oxidative stress (Morrow et al, 1995), an increased fruit consumption might have been redundant in reducing AAA hazard among never smokers if they already had a more optimal redox balance. Hemodynamic forces in infrarenal AAAs have been observed to further increase ROS-production, with an increased production the larger the aneurysm (De Keulenaer et al, 1998), which could explain why the inverse association with fruit consumption seemed to be more pronounced for rAAA than iAAA. No individual fruit was specifically associated with AAA hazard.

Alcohol

We observed that moderate alcohol consumption (5 glasses/week among women, and 10 glasses/week among men) was associated with a lower hazard of AAA diagnosis and/or repair in the entire study population, but not in a subcohort of participants free of CVDs. The most commonly consumed alcoholic beverages, i.e., beer for men and wine for women, were inversely associated with AAA in the entire population as well as in the CVD-free subcohort. Furthermore, we observed that a moderate consumption of alcohol was associated with a smaller AAD among men.

Moderate alcohol consumption is inversely associated with other cardiovascular morbidities, such as coronary heart disease and stroke (Mukamal et al, 2003b; Mukamal et al, 2005a; Ronksley et al, 2011b). Only two previous prospective studies of selected male populations have, however, investigated the relationship between alcohol consumption and AAA hazard. The first study, based on a population free of CVDs at baseline and during follow-up (Wong et al, 2007), observed a statistically significant trend towards a higher hazard of AAA with increasing alcohol consumption, with a statistically non-significant higher hazard among drinkers in the highest category of alcohol consumption (≥30 grams/d [mean, 46.1 grams/d], corresponding to ~17 glasses/wk), compared with those who did not consume alcohol. The other study included male smokers only (Tornwall et al, 2001), and reported no clear trend with total alcohol intake, although there was an indication of a J-shaped association (Mukamal, 2001; Tornwall, 2001). The lack of significance may be explained by a higher degree of oxidative stress among smokers (Morrow et al, 1995). In our population-based study, however, the association between alcohol consumption and AAA hazard did not differ by smoking status.

Total alcohol consumption (i.e. ethanol) did not seem to be associated with AAA diagnosis and/or repair among participants free of CVDs. The most commonly consumed alcoholic beverages (i.e. beer for men and wine for women) were, however, still inversely associated with AAA in this subgroup. A possible explanation for this observation might be the separate biological effects observed to be associated with ethanol and the polyphenolic content of alcoholic beverages.

Mainly, ethanol targets lipid regulation (Mukamal et al, 2005a), and it has been described that the genetic risk profiles for lipid factors and coronary heart disease were associated with prevalence of AAA (van 't Hof et al, 2013). Thus, when we censored CVD-cases during follow-up, analyses potentially disregarded from a population that would benefit the most from a regulation of lipids (Chiva-Blanch et al, 2012). Instead, the analysis might have been performed on a population where a regulation of lipids was redundant, without genetic predisposition for hyperlipidemia, CVD, or AAA. We did observe that hypercholesterolemia at baseline was associated with an increased risk of AAA detected at screening among men.

The polyphenolic content, mostly found in red wine, but also in white wine and beer (Alvarez et al, 2012a; Arranz et al, 2012), has been attributed a more general spectrum of favorable effects, such as effects on systemic inflammation (Estruch et al, 2004), inhibition of the NADPH oxidase that promotes oxidative stress in the aortic wall (McCormick et al, 2007b; Miller et al, 2002; Yajima et al, 2002b), and by affecting cellular redox state (Estruch et al, 2011b), and endothelial function (Tousoulis et al, 2008). This might explain why the association remained inverse for wine and beer even among participants without CVD.

Only 3.6% of men, and 2.2% of women, in the studied population were heavy drinkers (≥ 4 and ≥ 2 daily glasses, among men and women, respectively (Di Castelnuovo et al, 2006)), leading to limited statistical power to examine a possible relationship between heavy drinking and AAA hazard. An increased risk of AAA could, potentially, be mediated via hypertension (Taylor et al, 2009), as suggested by Wong et al (Wong et al, 2007). However, no clear association has been observed between a moderate alcohol consumption and hypertension (Stranges et al, 2004). Alcohol consumption is not recommended as a preventive approach for any disease given its potential adverse effects. The American Heart Association recommends a maximum consumption of no more than two daily glasses for men, respectively one for women (Goldberg et al, 2001).

Comorbidity and physical activity

We observed that CVD was associated with a larger mean AAD, and a higher risk of developing AAA, as was hypercholesterolemia. Diabetes at baseline was associated with a smaller mean AAD.

Findings are consistent with several studies on the matter. For instance, CVD has been associated with a higher AAA prevalence in most epidemiological studies (Lederle et al, 1997a; Pleumeekers et al, 1995; Svensjo et al, 2011). It is likely that CVD's are associated with a generally diseased vasculature, rather than actually causing AAA. Hypercholesterolemia was also associated with incident AAA in the Tromsø Study (Forsdahl et al, 2009), and historically elevated levels of LDL, total cholesterol, and triglycerides, were associated with AAA prevalence in the Norsjö Municipality Study (Wanhainen et al, 2005).

Furthermore, we observed that men who walked or bicycled for >40 min/day had a lower hazard of having an AAA at screening, as compared with those who almost never walked or bicycled. Although studies are scarce, an association between an increased physical activity and a lower AAA prevalence have previously been described in the Life-Line Screening study; those who exercised ≥1/week had a 14% decreased risk of having an AAA (Kent et al, 2010).

Methodological considerations

When designing a study, two sources of error need to be accounted for; random and systematic errors. Bias is another term for a systematic error and there are several different ways in which a study can be biased; through procedures used to select participants and from factors that influence study participation (selection bias), how variables are collected and measured (information bias), or if not controlling for some confounding factor. The random error is the degree of error left after all systematic errors have been accounted for, and are reduced with increasing study size, while systematic errors bias the results in a study regardless of its size.

Selection bias

Selection bias occurs when the study population fails to represent the population for which the study is intended to target, an error which can be introduced when planning, designing, and implementing a study. The results of a study are biased when the relation between a certain exposure and the disease differ in the studied population compared with the target population.

Selection bias can be controlled for when the distribution of variables influencing selection, the exposure, and the outcome, are measured on all study participants, and is known in the whole target population. As previously mentioned (*Participants and Methods*), the distribution of age, educational level, and Body Mass Index, in the COSM and SMC 1997 are representative of the Swedish population in 1997. The proportion of current smokers in the two cohorts were also similar to the proportion of daily smokers in a national survey on living conditions in 1996/97 performed by Official Statistics Sweden (Official Statistics Sweden, 1997). Furthermore, the incidence of AAA diagnosis and/or repair between 1998 and 2005 in the SMC and COSM corresponded to the incidence in Mid-Sweden (the same study area) between 1990 and 2005 (Hultgren et al, 2012). We did, however, observe that the prevalence of AAA among men between ages 65 to 75 was lower than that of the general Swedish population, which could indicate that non-responders were at higher risk of AAA than those who participated in the COSM – which could indicate a so called *non-response bias*.

However, if variables influencing selection are measured among all study participants and these variables precede exposure and outcome, or if the probabilities of selection for each level of these variables are known, controlling for an error in selection of the study population can be achieved. All participants in the two population-based cohorts were followed prospectively, and did not have a clinical diagnosis of AAA at the start of the study. Thus, an error in selection truly influencing the estimated results would imply that the inclusion to the study itself was associated with the exposures and AAA disease, or that responders differed biologically from non-responders, which is a rather unlikely scenario.

One way in which an error in selection could be introduced during study implementation is through a differential loss of follow-up between exposed and unexposed individuals. However, this possibility was minimized since follow-up through linkage to population-based registers was nearly complete (Ludvigsson et al, 2011; Nilsson et al, 1994; Venermo et al, 2015), and all participants in the subgroup of screened men had their AAD measured.

Thus, even if arguing that baseline characteristics of the cohort participants differed from those of the general population, it is rather unlikely that the observed results in the studies of this thesis can be explained by an erroneous selection of study participants.

"Elevating the importance of representativeness is a fallacy that has plagued epidemiologic studies for decades" – Kenneth J. Rothman (Rothman, 2012).

Information bias

Information bias refers to the error that occurs when collected data that are to be analyzed are faulty. One common information bias is misclassification, a bias which originates from the failure to perfectly detect disease and/or exposure (e.g. participants may be faulty classified as un-exposed or not having the disease when the opposite is actually true). The proportion of positives correctly identified as such is called sensitivity (i.e. quantifying the chance that false negatives are avoided), while specificity is the proportion of negatives correctly identified as such (i.e. quantifying the chance that false positives are avoided). In most studies, one assumes a certain degree of misclassification given that perfect tools to gather data is utterly uncommon. Misclassification is generally divided in two major types; differential and non-differential. Differential misclassification occurs when the misclassification differs between groups that are to be compared, which could bias the estimated results towards any direction. In non-differential misclassification, the proportion of faulty data is the same between groups that are to be compared, and results can either be biased, or not affected.

Misclassification of exposures

Self-administered data on lifestyle variables used in the studies of this thesis are likely to be associated with some degree of misclassification. The most common causes of misclassification in a questionnaire would be that of a recall bias, or a reporting bias. Recall bias could occur if participants are aware of their disease and, thus, more likely to report an exposure that they know, or think, could influence it. A reporting bias could occur if participants unknowingly "collaborate" with the researchers and become more likely to report an exposure if they think it is of interest (*obsequiousness bias*), if a case occurs within family and participants become more likely to report family history (*family aggregation bias*), or less likely to report an exposure if the question is perceived as embarrassing or socially undesirable (*un-acceptable exposure bias*). Furthermore, when utilizing FFQs, participants tend to report their current exposure, rather than their average exposure over the past year, and thus, may underestimate their intake (*mode for mean bias*).

Although most of the exposures used in the five studies of this thesis were validated, it is, for example, rather likely that individuals with large waist-circumferences or BMI-values, those with a high consumption of alcohol, and smokers, misreported their true measurements or habits. Furthermore, even though both registers and self-reported data were utilized for identification of comorbid disease at baseline, it is likely that not all participants with comorbidity were identified, especially not those who had angina pectoris, hypertension, or hyperlipidemia. However, participants with more severe cardiovascular diseases (e.g. myocardial infarction or ischemic stroke), and diabetes, were most likely identified through the IPR and the NDR, given the high sensitivity and specificity of those diagnoses.

Given that AAA most commonly is an asymptomatic disease, and that we did not have information of the participants' AAD at baseline, some participants may have had an AAA when reporting exposures. However, it is unlikely that the AAD at baseline would have any effect on the reporting of exposures, and since all exposures were prospectively collected, any potential misclassification of exposures was most likely non-differential with regards to AAA diagnosis/repair, and with AAD between 65 and 75 years of age.

Although the direction of a potential non-differential misclassification is never certain (with the exception of a binary exposure were estimates are biased towards the null), an underestimation of smoking habits and anthropometric measures would most likely lead to an underestimation of the true associations, and classification of failed quitters as past smokers would most likely reduce the estimation of the benefit associated with smoking cessation. Underestimation of alcohol, and dietary, consumption would most likely dilute the true associations. Misclassification of current consumers of alcohol as never or former drinkers could potentially drive the estimates towards any direction, given that the association between AAA and alcohol is not very well studied. However, the observed associations among participants who reported alcohol consumption should neither have been differentially misclassified according to AAA disease and, thus, most likely dilute the observed associations.

Misclassification of cases

In the studies which identified AAA through registers, there was no routine investigation of the participants' aortic diameters, which most likely is associated with some degree of under detection of asymptomatic disease among participants not classified as cases, although the completeness of utilized registers is considered high. That is, the sensitivity of AAA detected through registers was not 100%. However, a reduced sensitivity does most likely not affect observed estimates, given that such misclassification probably is non-differential (i.e. the misclassification itself does not depend on the exposure of interest), although the CI's may be assessed with a wider degree of uncertainty. If specificity is lacking (i.e. the AAA diagnosis, when assigned, is not always correct), estimates are likely to have been affected. AAA is a serious disease with a strict diagnostic criteria, and once an AAA has developed, it does not regress on its own. Hence, it is unlikely that a participant would be diagnosed with an AAA if he/she does not have an aneurysm. Furthermore, the validity of the Swedvasc register have been observed as high for AAA related procedures (Troeng et al, 2008; Venermo et al, 2015).

AAA deaths identified through the CDR are also likely to be under detected, given that autopsies are not performed very often. As previously described (*Methods, Ascertainment of AAA and follow-up of the cohorts*), autopsy rates in Sweden have declined, and are lower among women than men. Compared with men, the disease seem to be associated with higher risks of rupture among women (Sweeting et al, 2012; UKSAT, 1998b). Essentially, this could mean that a larger proportion of AAA related deaths among women remains unreported as compared to the proportion among men. This further strengthens the argument that the viability of screening among subgroups of women may require further investigation.

In attempt to increase the sensitivity of the register based outcome, we performed analyses restricting it to clinically relevant diameters, as larger diameters are less likely to be missed given that the frequency of symptomatic disease (e.g. rupture) also increases with diameter, and results did not change. The prevalence of such disease has been reported to be ≤0.1% at 65 years of age and approximately 1% at 70 years of age (Svensjo et al, 2011; Svensjo et al, 2014), and even less among women (Svensjo et al, 2013). As the introduction of AAA screening programs in 2006 most likely led to an increased diagnostic activity of AAA, we performed analyses by restricting the follow-up in Study I-IV to 31 December 2005, and the interpretation of main results did not differ substantially.

In Study V, estimates were rather similar among women and men with ≥20 pack-years of smoking when restricting the outcome to clinically relevant diameters, and when the end of follow-up was restricted to 31 December 2005 (screening of women with AAA risk factors started in Västmanland in 2007). This might be explained by low statistical power due to the low number of female patients with large AAAs, and the low number of accumulated AAAs in women during that relatively short follow-up. On the other hand, it may also indicate that AAA was differentially misclassified between men and women across different strata of smoking, since AAA was identified through registers in that study. However, when the end of follow-up was set to 31 December 2005, the age-standardized AAA incidence among smoking women was still double that of never smoking men.

In the last study of this thesis (Study V), only men that underwent ultrasound screening for AAA between 65 and 75 years of age were included and, thus, the sensitivity and specificity of the outcome in that study is likely to be higher than in the other studies. However, some issues with the outcome classification in this study do deserve attention. As previously discussed, no baseline assessment of the aortic diameter was undertaken and, thus, participants may already have had an AAA at time of exposure assessment. The mean age at baseline for the cohort that was screened was 55 years. In the Tromsø Study (Forsdahl et al, 2009), the prevalence of AAA was reported as 1.3% between 15 and 54 years of age, and 2.4% between 55 and 59 years of age. In the ADAM study (Lederle et al, 1997a), the prevalence of large AAAs (≥40 mm) between 50 and 54 years of age was 0% among non-smokers, and 0.3% among smokers. Among those aged 55 to 59 years, corresponding prevalences were 0%, and 0.9%, respectively, in that study. Thus, the proportion of participants with an AAA at baseline was likely to be very low. Furthermore, the AAD does not decrease over time and a participant with an AAA at baseline would still be classified as a case at the time of screening. Given that the potential misclassification of exposures is likely to be non-differential with respect to AAD at baseline, not excluding participants with an aneurysmatic diameter at time of exposure assessment is unlikely to have any substantial impact on the observed results.

Furthermore, the repeatability of AAD measurements using ultrasound is not perfect. With a reported inter observer variability of 2.0 mm (95% CI, ±4.0 mm) for the LELE-method, respectively 2.7 mm (95% CI, ±5.4 mm) for the OTO-method, a 29 mm aorta measured by one technician could be measured as 31 mm or more by another (Gurtelschmid et al, 2014). Since such error would go in both directions, it is possible that the sensitivity and specificity of AAA as a binary outcome could both have been affected among participants close to the diameter limit of an aneurysm. Although the impact of such error is never certain, it is likely to be non-differential with respect to baseline measurements of lifestyle exposures. In an attempt to address this issue, however, we performed additional analyses using ≥35 mm as outcome. Although those analyses suffered from a loss of power due to fewer cases (n=91), results did not differ substantially from those of the main analyses. In analyses where AAD was analyzed as a continuous outcome, ultrasound measurement errors would most likely only dilute the true results. Unfortunately, this analysis could not be performed on all screened participants as the measured diameter was not registered among 5706 participants with an AAD <25mm.

Other information biases

One limitation that may propose a risk for biased estimates is if participants changed their lifestyle during follow-up. To investigate to which degree participants had changed their habits; we utilized data from another questionnaire sent out to women in the SMC, and men in the COSM, still alive and living in the study area in 2009 (response rate 70%, respectively 54%, for the COSM and SMC 2009). Only 38% of current smokers in 1997 reported that they still smoked in 2009, and 0.4% of never smokers reported that they had started to smoke. Furthermore, between 1997 and 2009, the proportion of men and women remaining in the same, or changing to an adjacent, quartile of consumption was 69% for fruits, 83% for vegetables, and 77% for meat. Interchanging between extreme quartiles occurred among 8% for fruits, 3% for vegetables, and 6% for meat. Thus, participants had quit smoking to a large extent during follow-up, which also is seen nationally (Patja et al, 2009), and it seems as there were minor differences in intake of fruits, vegetables, and meat, between 1997 and 2009.

A change in lifestyle over follow-up would, however, most likely also be non-differential with respect to AAA risk, given that we only used incident diagnosis and/or repair. With regard to the observed estimates, an underestimation of the association between current smoking and AAA risk could most likely be expected if current smokers ceased to smoke during follow-up. Furthermore, several studies have previously observed that smoking affects the risk of AAA even 10 to 20 years after cessation and it is, therefore, rather unlikely that smoking cessation during follow-up would affect observed results substantially.

Furthermore, exposure may be correctly classified, but influenced by subclinical stages of a disease or chronic illness (*protophatic bias*), increasing the likelihood of undergoing AAA examination. For example, smokers may have developed COPD and thus be more prone to quit smoking, but their regular contact with healthcare increases their chance of being diagnosed with AAA. The assumption of exposure anteceding AAA might also be ambiguous if a participant had an asymptomatic AAA at baseline. To account for these issues, we performed sensitivity analyses by excluding the first three years of follow-up and results did not change. Furthermore, if participants with a risky behavior, such as those with heavy alcohol consumption, quit their consumption because of a disease, they would be labelled as former drinkers, but still be at higher risk of being examined for AAA. This so called *sick-quitter bias* was accounted for by not including former and never drinkers in continuous analyses of alcohol consumption in Study IV. However, results did not change when those groups were included in the analyses.

Confounding

Confounding can be simply put as a "confusion of effects", and occurs when the effect (or hypothesized effect) of an exposure of interest is confused with the effect of another variable. For example, in Study IV, alcohol consumption initially seemed to be associated with an increased risk of AAA. However, consumers of alcohol also smoked to a larger extent than low- or non-consumers. When alcohol consumption was adjusted for smoking habits, alcohol consumption was observed to be inversely associated with AAA risk, that is, the association between alcohol consumption and AAA was "confounded" by smoking habits. The presence of a confounding variable could drive estimations toward any direction, or null. However, the confounding variable must be associated with both the exposure and the outcome (not as an effect of the disease, but as a cause or proxy for a cause) in order to be a true confounder. Furthermore, a confounder must not lie in between exposure and outcome in the causal chain of disease development, for if so, it is an intermediary factor. For example, the inflammation of the aortic wall thought to be caused by smoking is an intermediary in AAA development. A simple example of the relationship between confounders and intermediary factors in a hypothetical causal chain of AAA development is illustrated in Figure 21.

There is no golden standard for how to identify a potential confounder, which factors to adjust for in a statistical model, or how they should be adjusted for. However, inclusion of confounders should be based on prior knowledge of the disease and the exposure, as well as the statistical characteristics of the population of interest. In many cases, factors known to be associated with the disease are included as confounders even though they are not associated with the exposure of interest. Estimates can also be affected by residual confounding if the models are not adjusted for all variables that are truly confounding the observed association, or if there is a measurement error of those variables.
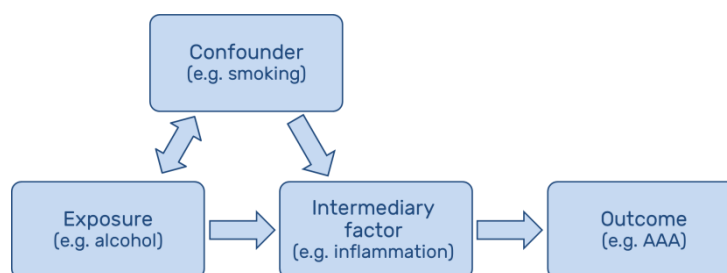

Figure 21. Example of the relationship between an exposure, confounder, and intermediary factor, in a hypothetical causal chain of an outcome.

Several different ways of controlling for confounding exists. One way is to add the confounder as a covariate in the statistical model. In multivariable analysis, the estimate of an exposure will then reflect the effect of that exposure assuming that all participants belonged to the reference category of the other covariates added to the model. Sometimes, there might be an interaction between two variables (previously discussed in *Methods, Assessment of interactions*). An interaction would imply that the joint effect of the two combined produce a different effect than the two would do alone. In Study I, we observed a significant interaction between sex and smoking status, and years since smoking cessation. In separate analyses by sex, the absolute risks of AAA were higher among men for each specific strata of smoking. However, women seemed to have higher relative risks due to smoking, and experienced a more rapid decline in excess risk following smoking cessation. Thus, it seems as if smoking women were more sensitive to current smoking, regarding the risk of AAA.

Another way of controlling for confounding is to stratify the results by different levels of the confounding variable, or by excluding participants exposed to it. In randomized controlled trials, the issue of confounding is effectively solved by the randomization process of the exposure itself, since no factor is associated with the exposure and could, thus, not be a confounding factor.

In the studies of this thesis, confounding was partially controlled for by excluding participants with cancer at baseline. Cancer might not increase the risk of AAA alone, but it could increase the chances of a participant being diagnosed with AAA. Furthermore, lifestyle-related exposures may be radically affected by a cancer diagnosis, and not reflect the true exposure during the past year. While this is very common within nutritional epidemiology, exclusion of participants with cancer was also necessary in order to remain consistent as all women who developed cancer after returning the 1987 questionnaire were denied to participate in the SMC 1997 (as the cohorts originally were designed to study cancer).

In Study I-IV, participants with missing information on the primary exposures of interest were excluded. In Study II, those with extreme values of BMI and waist circumference were also excluded to limit the possibility that extreme values had an impact on the observed results. In all of the studies, multivariable models adjusted for potential confounders were presented. For example, if a participant consumed a high amount of fruits and vegetables, they might also be more likely to have a healthier lifestyle in general (healthy user bias), and the association observed between fruit consumption and AAA risk might have been confounded by some other lifestyle-related variable. Therefore, we adjusted the models for other dietary variables (i.e. meat, fish, and wholegrain consumption), and for levels of physical activity, and the results did not change. If estimates for fruit consumption in Study III reflected a healthy behavior in general, we would have expected an association with vegetables to. Likewise, in Study II, if waist circumference was associated with AAA detection rather than the etiology of the disease, an association with BMI would have been expected.

We also controlled for confounding by limiting the analyses to participants without certain comorbidities, at baseline and during follow-up, as these participants might be more likely than others to undergo AAA examination. In most of these analyses, results remained the same with the exception for the observed null association of total alcohol among participants free from CVDs (previously discussed in *General discussion, Alcohol*). There was no formal evidence of an interaction between alcohol consumption and CVD at baseline, but the censoring of CVD-cases during follow-up did seem to yield a change of the observed estimates.

Related to the issue of baseline lifestyle changing over follow-up time, the degree of confounding can also change over time. For example, smoking participants with a high baseline consumption of fruits could have been more prone to quit smoking over follow-up, compared with smoking participants with low baseline consumption. Such confounding could potentially affect the estimates toward any direction, and without longitudinal measurements of exposures over follow-up, controlling for it is hard. Although the observed hazards of exposures were proportional over time, testing the Scaled Schoenfelds residuals is not accurate enough to ensure that this was not the case. However, the test could give an indication that the observed estimates were not substantially biased by such confounding. When analyzing separate time spans of follow-up in the different studies, results did not change.

Finally, survival bias could also be a cause of concern regarding inference of observed estimates. Such bias is the logical error of concentrating on participants that survived during follow-up, overlooking those that did not. Thus, false inference can potentially be drawn if some exposure leads to an increased longevity, and thereby an increased time at risk for developing AAA. For example, low consumers of fruit and vegetables might experience a premature death as compared with those with a high consumption, and thereby reduce their time at risk for development of AAA. Thus, the effect of consumption of fruits and vegetables at baseline could have been underestimated. To evaluate this issue, a competing risk analyses was performed in Study III with all-cause mortality as competing risk. However, this analysis did not alter the results.

CONCLUSIONS

The results presented in this thesis add to the scientific evidence regarding the associations between modifiable lifestyle-related factors and abdominal aortic aneurysm (AAA) disease. More specifically, the following is concluded:

- The incidence of AAA was higher among men for all specific smoking strata and smoking was associated with an increased risk of AAA among both men and women. Current smoking may affect women to a larger extent than men, regarding risk of AAA.

- Obesity may increase the risk of AAA. Whether central, or total, obesity is of most importance remains unknown.

- Consumption of fruits may reduce the risk of AAA.

- A moderate consumption of alcohol may reduce the risk of AAA.

- Among men, lifestyle and comorbidity may be of importance regarding risk of AAA disease detected at screening, and may be directly associated with abdominal aortic diameter.

FUTURE RESEARCH

Research on the epidemiology and pathophysiology of AAA can essentially be broken down into three important questions; who develops an AAA, what factors affects its growth, and what causes the aneurysm to eventually rupture. By answering these questions, one would be able to accurately identify AAA patients, determine who is at high risk of rupture, and find new ways of treating the disease, perhaps even without surgical intervention.

The findings in this thesis support that modifiable lifestyle-related factors may play a role in primary prevention of abdominal aortic aneurysm (AAA), i.e. who develops an AAA. The associations between obesity, and alcohol consumption, and risk of AAA were very scarcely investigated. No previous study had prospectively investigated the association between consumption of fruit and vegetables and risk of AAA, or the sex-specific associations of smoking status, and cessation, in two cohorts where men and women originated from the same study area.

With the data we have collected, we plan to further investigate possible associations between other aspects of lifestyle and diet (e.g. consumption of fish, meat, grains, and sweets, and physical activity and inactivity) and risk of AAA disease.

In order to find means of decreasing AAA growth rate, and to be able to give lifestyle advices to AAA patients, investigation of whether lifestyle-related exposures affect the rate of growth in small AAAs (to avoid or delay intervention), rate of rupture, and the outcome after AAA repair, merit further investigation. This could, for example, be achieved by interventional studies in AAA patients.

Studies focusing on whether different factors are associated with different steps in AAA pathophysiology also merit investigation in future studies.

Furthermore, investigation of lifestyle-related exposures that may interact with hereditary risk factors of AAA is an area of research where evidence is lacking. Identification of such factors may further enable individually based lifestyle advices to AAA patients. For example, 9p21 variants have been shown to promote AAA. Previous studies observed an interaction between fruit intake and the 9p21-chromosome regarding risk of myocardial infarction, and a diet high in fruit have been associated with reduced risk of myocardial infarction in individuals with polymorphism on that chromosome. Thus, the observed beneficial effect of fruits on AAA risk may also be influenced by such diet x gene interaction and merit further attention.

Interactions between different risk factors, life-style related and genetic, modifiable and non-modifiable, need to be further investigated. Some interesting interactions were identified in this investigation, such as the fact that women were relatively speaking more sensitive to smoking than men. Although the main clinical message of this finding is smoking cessation, these interactions give us more understanding of the pathophysiology of AAA.

More studies are in general needed regarding AAA disease in women. In the light of the observed findings of this thesis, investigation of whether targeted screening among subgroups of women at risk of AAA would benefit from screening need to be assessed in randomized trials and health economy research. With the data we already have gathered, we plan to investigate hormonal factors that may be prospectively associated with AAA risk (e.g. age at menopause, menarche, and hormone replacement therapy). With update of data over time, there is a possibility that we will observe enough AAA cases to also study factors associated with risk of screening-detected AAA among women in the future.

Last, even though participation rates are high compared with other screening programs, studies focusing on increasing participation rate in AAA screening are warranted. Some studies have reported indications of a larger proportion of smokers among those not attending AAA screening (which we also have observed in preliminary analyses), but there are no available studies with smoking data on an individual level. Since there is a risk that non-participants may harbor an AAA to a larger extent than those who do attend screening, we plan to perform a study investigating whether lifestyle-related and socioeconomic factors are prospectively associated with participation in AAA screening.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Pulsåderbråck i buken, eller bukaortaaneurysm, är en långsamt växande, sjuklig vidgning av den del av stora kroppspulsådern (aortan) som löper i buken. Sjukdomen drabbar oftast äldre, rökande män. Risken med ett pulsåderbråck är att det växer sig så pass stort att det till slut spricker, vilket oftast resulterar i en stor blodförlust ut i fri bukhåla och en nästan oundviklig död som resultat. Då ett växande aneurysm ofta inte uppvisar några symtom förrän kroppspulsådern har spruckit har man börjat införa screening av sjukdomen i de flesta delar av världen. Genom att undersöka alla män i 65 års ålder med ultraljud är syftet med screeningen att upptäcka sjukdomen i tid för att kunna övervaka dess tillväxt. Då bukaortaaneurysm är så pass ovanligt förekommande hos kvinnor är det varken ekonomiskt, eller kliniskt, motiverat att screena alla kvinnor. Däremot har det föreslagits att man eventuellt borde screena alla äldre rökande kvinnor, men belägg för detta saknas.

Man opererar ett pulsåderbråck när det växt sig så pass stort att risken för att aortan spricker är högre än de potentiella risker det innebär med en operation. Operationen syftar till att utesluta pulsåderbråcket från cirkulationen och därmed minimera risken att det fortsätter växa. Man kan antingen åtgärda detta med en öppen operation, där man syr in ett så kallat graft, eller i röntgengenomlysning, där man för in ett stent inuti aorta via artärerna i ljumskarna.

Förutom rökstopp finns det egentligen inga medicinska behandlingsmetoder för att sänka tillväxthastigheten av ett upptäckt pulsåderbråck. Genom att identifiera livsstilsfaktorer som eventuellt påverkar risken att drabbas av sjukdomen kan man lära sig mer om hur sjukdomen uppstår, och eventuellt komma närmare en medicinsk behandlingsmetod som skulle kunna sänka tillväxthastigheten för ett upptäckt pulsåderbråck.

Till grund för denna avhandling ligger två stora populationsbaserade kohorter med svenska medelålders män och kvinnor; Kohorten över Svenska Män (COSM), och den Svenska Mammografi Kohorten (SMC). SMC initierades 1987 då alla kvinnor som blev inbjudna till mammografi, födda mellan 1914 och 1948 och bodde i Västmanland eller Uppsala län, fick fylla i ett frågeformulär med diverse frågor om livsstil och sjukdomar. Hösten 1997 skickade man sedan ut ett nytt utvidgat frågeformulär till alla kvinnor som fortfarande levde och bodde kvar i studieområdet. Under hösten 1997 skickades även ett liknande formulär ut till alla män i Västmanland och Örebro län, födda mellan 1918 och 1952, som då bildade COSM. Tillsammans består de två kohorterna av ca 85,000 män och kvinnor som var mellan 45 och 83 år gamla 1997. Genom att följa kohorterna över tid kunde vi sedan identifiera vilka män och kvinnor som utvecklat pulsåderbråck i buken, och på så sätt räkna på risken att drabbas av sjukdomen beroende på vad man hade för livsstil 1997.

I det första delarbetet undersökte vi den könsspecifika risken att drabbas av bukaortaaneurysm beroende på rökstatus, hur mycket man hade rökt, och hur många år sedan det var man eventuellt hade slutat. Vi fann att män hade högre absolut risk att drabbas av sjukdomen oavsett rökstatus, men däremot verkade kvinnor relativt sett vara känsligare för att vara aktiva rökare än männen. Rökande kvinnor hade till och med högre risk än icke-rökande män. Vi fann även att kvinnor som slutade röka halverade sin risk att drabbas av sjukdomen i princip dubbelt så snabbt som männen gjorde, vilket inte kunde förklaras av att män och kvinnor hade rökt olika mycket. Eftersom man screenar icke-rökande män för sjukdomen kan man därför tänka sig att det även vore lönt att screena rökande kvinnor, men för att fastställa detta krävs ytterligare studier på området.

I det andra delarbetet undersökte vi risken att drabbas av bukaortaaneurysm beroende på fetma. Vi fann att bukfetma (dvs ett ökat midjemått) var starkare kopplat till sjukdomen än vad total fetma (dvs ökat BMI) var. Vi undersökte även huruvida frukt-, grönsaks- och alkoholkonsumtion påverkade risken för sjukdomen i det tredje, respektive det fjärde delarbetet. Vi fann att ett ökat intag av frukt, men inte grönsaker, var kopplat till en lägre risk för sjukdomen. Vad gäller alkohol fann vi att en måttlig alkoholkonsumtion (ca 5 glas i veckan för kvinnor och 10 för män) var kopplat till en lägre risk att drabbas av sjukdomen hos de som inte blev hjärt- och kärlsjuka under studiens gång. Vi fann även att en måttlig konsumtion av öl hos män, och vin hos kvinnor, var kopplat till en lägre risk att drabbas av sjukdomen, vare sig man drabbades av hjärt- och kärlsjukdom under studiens gång eller ej.

I det femte och sista delarbetet identifierade vi alla män som hade screenats för sjukdomen mellan 65 och 75 års ålder och tog reda på vad deras exakta aortadiameter var vid screeningtillfället. I det arbetet fann vi att rökare, de hjärt- och kärlsjuka och de med höga blodfetter, hade en högre risk att ha sjukdomen vid screeningtillfället. Vi fann även att total fetma (dvs högt BMI) var kopplat till en högre risk att drabbas av sjukdomen. De som gick eller cyklade mer än 40 minuter per dag hade en lägre risk att ha ett bukaortaaneurysm, jämfört med de som nästan aldrig gick eller cyklade. Vi fann även att rökning, hjärt- och kärlsjukdom och högt BMI, var kopplat till en större diameter på aortan, samtidigt som en måttlig alkoholkonsumtion och diabetes var kopplat till en mindre diameter.

Sammanfattningsvis indikerar resultaten i denna avhandling att ens livsstil påverkar risken att drabbas av bukaortaaneurysm. Rökare löper en högre risk, likaså de med hjärt- och kärlsjukdom. Kvinnor verkar vara känsligare för aktiv rökning och skulle eventuellt gynnas av att inkluderas i ett screeningprogram för bukaortaaneurysm. Fetma verkar vara kopplat till sjukdomen men det råder tvivel huruvida bukfetma eller total fetma är det som är starkast kopplat. En ökad konsumtion av frukt, en måttlig konsumtion av alkohol, och ökad fysisk aktivitet sänker eventuellt risken att drabbas.

Det är av intresse att även ta reda på om en förändrad livsstil kan påverka tillväxthastigheten i screeningupptäcka pulsåderbråck, och på så sätt sänka risken för att man eventuellt skulle behöva opereras. För att ta reda på detta krävs dock fler studier på området.

ACKNOWLEDGMENTS

Many people deserve my great and humble appreciation for their contributions to this thesis, and for their support and encouragement during these years.

My principal supervisor, Professor **Alicja Wolk**. Thank you for giving me this opportunity, everything you have taught me, and for being an outstanding supervisor and mentor throughout these years. Thank you also for all the interesting discussions.

My co-supervisor, Professor **Martin Björck**. Thank you for sharing your experience and for everything you have taught me about vascular surgery research. You have been a superb supervisor, invaluable for this project and my future scientific and medical career. I doubt anyone is as committed, and as quick in replying to questions, as you are.

My co-supervisor, Associate professor **Susanna C. Larsson**. Thank you for sharing everything you know, for your commitment in this project, and for always being available. You, if anyone, know how to produce high-quality research in high quantities.

My co-authors; **Omid Sadr-Azodi** for recruiting me to the unit and the contributions you have made to my scientific career, **Nicola Orsini** for the invaluable guidance and knowledge you have shared in statistics and STATA-coding. **Anders Wanhainen, Adam Bersztel, Ken Eliasson,** and **Anders Hellberg**, thank you for your constructive criticism, for sharing your knowledge on abdominal aortic aneurysm, and for the help with data collection. To all of you, I am grateful for the invaluable contributions you have made to the studies of this thesis.

My past and present colleagues at the Unit of Nutritional Epidemiology. **Viktor Oskarsson**, with whom I have shared office, without your almost pathological thoroughness, more than one faulty statement and figure would have found its way in to this thesis. **Niclas Håkansson** for keeping track of our data. Many thanks also to **Andrea Discacciati, Andrea Bellavia, Alessio Crippa, Daniella Di Giuseppe, Alice Wallin, Susanne Rautiainen Lagerström, Bettina Jullin, Agneta Åkesson, Camilla Olofsson, Ann Burgaz, Thanasis Thektonidis, Laura Thomas, Holly Harris, Jinjin Zheng Selin, Mimi Throne-Holst, Becky Leung, Iffat Rahman, Lollo Sjöholm, Frej Stilling,** and **Charlotte Bergqvist,** it has been a privilege to work with you during these years.

My past and present colleagues at the Section of Vascular Surgery, Södersjukhuset, and the SOSVASC-group. **Peter Gillgren, Anneli Linné, Claes Skiöldebrand, Bengt Berg, Magnus Jonsson, Johnny Steuer, Jonas Malmstedt, Bertil Friberg, Fredrik Sartipy, Christian Smedberg, Sayid Zommorodi, Malin Nyberg Isacsson, Malin Jägestedt, Andreas Älgå,** and all **nurses** and **assistant nurses** at ward 57, for always believing in me, supporting me and welcoming me with open arms at and outside the clinic, and for everything you have taught me about general and vascular surgery. Thanks also to everyone else at the Department of Surgery at Södersjukhuset.

Mamma **Annika** och pappa **Wolter**, utan er hade det ju inte blivit så mycket av den här avhandlingen. Stort tack för all support och uppmuntran ni har gett mig genom åren och tack för det evinnerliga slit ni lagt ner på att vi ska ha det så bra som vi har. Mina syskon, **Anna** och **Oscar -** tack, tack! Morfar **Sam-Magnus**, tack för allt du gjort och jag vet att du och mormor **Margit** hade granskat den här avhandlingen noggrannare än någon annan. Tack också till **Susanne, Alexandra** och **Francis** som tar hand om farsgubben. Sist men inte minst **Maria**, jag vet inte hur detta hade gått utan dig, du har hjälpt och stöttat mig så sjukt mycket mer än vad du tror i skrivandet av den här.

Many thanks also to all my family, friends, and colleagues that I have failed to mention here!

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