The epidemiology of abdominal aortic aneurysm and natural history of type II endoleak after endovascular aneurysm Repair

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By

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Abstract

Abdominal aortic aneurysm is an important cause of death globally, however, its impact is less today than two decades ago due to a decline in AAA mortality. Within the same timeframe changes have occurred to the way that AAA may be treated, for example an increasing use of endovascular surgical techniques.

Type II endoleak is one of the most common complication of endovascular aneurysm repair. The sequela of having a type II endoleak is however unknown. My objectives within this thesis were to analyse causes of the decline in aneurysm mortality being seen in many developed countries using data derived from the World Health Organisation and investigate short/medium term outcomes of patients with type II endoleak at a single centre in the United Kingdom.

Through these studies I have demonstrated a robust association between trends in established cardiovascular risk factors and mortality from AAA suggesting that a reduction in the global burden of high cholesterol (P=0.0082), hypertension (P=0.028) and smoking (P=0.017) have led to a drop in AAA mortality. Aneurysm rupture in patients with an isolated type II endoleak appears to be rare occurring in less than 1% of all literature reported type II endoleaks and no ruptures were recorded in patients with type II endoleak followed up prospectively. Patients with isolated type II endoleak demonstrate equivalent aneurysm related mortality to those without, however, there is a strong independent association between type II endoleak and 5mm of aneurysm sac expansion (P=0.0001). A conservative strategy to the treatment of type II endoleak appears to be safe and given time isolated type II endoleak appear to have a good chance of spontaneously resolving without the need for invasive intervention. For those patients with type II endoleak and 10mm of aneurysm sac expansion, further research is needed to investigate the risk *versus* benefit of intervention.

Statement of Authenticity

I certify that the work within this thesis is of my own creation and represents my own efforts and ideas, with the following exceptions. The ELISA work was undertaken with the assistance of Dr Ana Verissimo and Jonathan Barber. Professor John Thompson assisted with the linear in-errors regression. I understand that use of another individuals work without acknowledgement is plagiarism, and is grounds for disqualification. I certify that the writing of this thesis was solely by me, and is my original work.

David Sidloff

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List of Abbreviations

AAA – Abdominal Aortic Aneurysm
ASM – Age Standardised Mortality
CEUS – Contrast Enhanced Ultrasound
CI – Confidence Interval
Ch - EVAR – Chimney endograft
COPD – Chronic Obstructive Pulmonary Disease
CT – Computerised Tomography
CTA - Computerised Tomography Angiogram
DUSS –Duplex Ultrasound
ELISA – Enzyme Linked Immunosorbant Assay
EVAR – Endovascular Aneurysm Repair
fEVAR - Fenestrated EVAR
F1+F2 - Prothrombin fragments
FBG – Fasting Blood Glucose
Gd-DTPA - Gadolinium diethylenetriamine penta-acetic acid
GWAS – Genome-Wide Association Study
HDL – High Density Lipoprotein
IFU – Instructions for use
LDL – Low Density Lipoprotein
LRP1 – Low Density Lipoprotein Receptor Related Protein
IQR – Interquartile Range
LA – Large Aneurysm (>55mm)
MAPK – Mitogen-Activated Protein Kinase
MASS – Multicentre Aneurysm Screening Group
MD – Mean difference
MMP – Matrix metalloproteinase
MRA – Magnetic resonance angiography
MRI – Magnetic resonance imaging
OSR – Open Surgical Repair
PAP – Plasmin anti-plasmin complex
PAD – Peripheral Arterial Disease
PAI – Plasminogen Activator Inhibitor
PO – Post-operative
RCT – Randomised Controlled Trial
ROC – Receiver Operator Characteristic
SNP – Single Nucleotide Polymorphism
SD – Standard Deviation
SEM – Standard Error of the Mean
SI unit – Systeme Internationale
SMD – Standardised Mean Difference
TAA – Thoracic Aortic Aneurysm
tPA – Tissue Plasminogen Activator
TAT – Thrombin anti-thrombin Complex
UK – United Kingdom

USA – United States of America
USS – Ultrasound Scan

Chapter 1: Introduction

1.1 Aims

Many of the risk factors for abdominal aortic aneurysm (AAA) for example hypercholesterolemia, hypertension and smoking have had well described epidemiological changes over the last decade. These changes have come about with a focus on public health medicine in the United Kingdom and most developed economies to reduce the global burden of cardiovascular disease for example myocardial infarctions and stroke. In the first chapter I discuss the relevant risk factors of AAA and investigate trends in the most important of these risk factors, namely smoking. Abdominal aortic aneurysm which I will describe in this chapter may be described as a local manifestation of the generalised disease that is cardiovascular disease and so it is the hypothesis of the first part of this thesis, that the public health measures introduced to reduce the burden of cardiac and cerebral vascular disease, have also reduced the burden of AAA. I investigate the relationship between changes in relevant cardiovascular risk factors and the number of people dying from AAA using an internationally validated source. Furthermore, I examine how changes in these same risk factors relate to thoracic aortic aneurysm mortality as it has been proposed within the literature that AAA is a patho-physiologically different disease to thoracic aortic aneurysm.

Over the timeframe of these epidemiological changes there has been a paradigm shift in the surgical treatment of AAA. I discuss in the remaining chapters the introduction of endovascular aneurysm repair including some of the benefits and new challenges that this has brought with it. Type II endoleak is arguably one of the most challenging complications of EVAR due to the uncertainty surrounding its management. I assessed outcomes in

patients with this complication at a vascular tertiary referral centre with the aim of investigating its gold standard management.

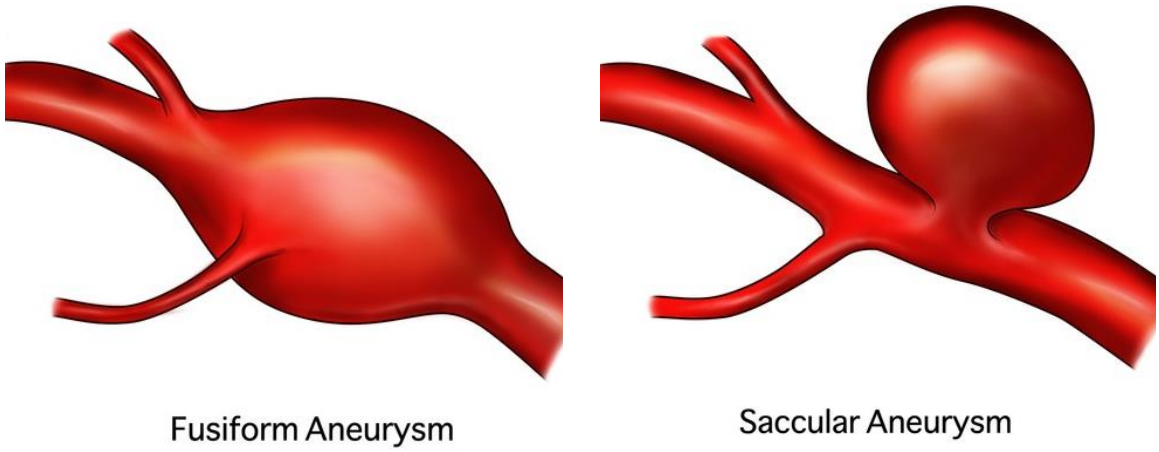
1.2 Abdominal Aortic Aneurysm

Abdominal aortic aneurysm (AAA) is a significant burden on healthcare globally[1] and may be defined as an increase in aortic diameter of 50% or more in relation to an adjacent normal aortic segment. The word aneurysm is derived from the Greek word aneurysma meaning 'widening' and the first written evidence of their existence was recorded in the 'Book of Hearts' from the Eber Scolls of ancient Egypt, dating back to 1550 BC. The first clear description of aneurysms including a mention of such lesions potential for rupture was recorded in the second century by Antyllus[2], a Greek surgeon living in Rome. Antyllus is also credited with performing the first attempt at a AAA repair having described ligation of the aorta above and below an aneurysm, followed by incision into and emptying of the sac. Unfortunately this procedure was universally fatal[3]. In 1554 Vesalius produced one of the most influential books on human anatomy based on cadaveric dissection 'De Humani Corporis Fabrica' (*On the Structure of the Human Body*), a year later providing the first accurate diagnosis and illustrations of AAA pathology before becoming physician at the court of the holy roman emperor Charles V.

The aorta is the largest artery in the human body, beginning directly after the aortic valve, and terminating at its bifurcation into the common iliac arteries (at the level of the 4th lumbar vertebra in 70% of patients). Where the aorta passes through the diaphragmatic hiatus it becomes known as the abdominal aorta. After the renal arteries the abdominal aorta becomes known as the infra-renal aorta and this is the commonest site for AAA, the vast majority of which are fusiform in shape (Figure 1.1). Other types of aneurysm exist for example saccular aneurysms which are approximately spherical in shape. Aneurysms may also be defined as true (involving the tunica intima, tunica media, and tunica adventitia of

the arterial wall) for example most AAA, or false (a collection of blood around a vessel confined by the surrounding tissue) and can occur secondary to atherosclerosis and/or infection (mycotic). They are also related to dissections (where blood is diverted from its usual location within the lumen of the aorta, into a false lumen within the media through a tear in the intima) and connective tissue diseases for example Marfans syndrome[4] or Ehlers Danlos Syndrome[5].

Figure 1.1, Example of a fusiform and saccular aneurysm, reproduced with permission from Withers *et al*[6].



Normal infrarenal diameter is approximately 1.9cm in males and 1.6cm in females[7]. Practically a measurement of greater than 3cm in any axial diameter is taken to be diagnostic for AAA. AAA cause approximately 4000 deaths per annum in the United Kingdom[8], however, 90% of AAA are asymptomatic until the onset of complications, the most serious of which is rupture[9]. The overall mortality rate following rupture of AAA is approximately 90%, however, this figure may even be higher as many patients dying from AAA rupture often do not undergo formal post-mortem examination[10]. Most AAA are characterised by the presence of a non-occlusive mural thrombus[11]. This thrombus may acutely occlude the vessel (more common at other sites for example aneurysms of the popliteal artery) or may break away in fragments (embolise) causing acute distal ischaemia.

Risk factors

Risk factors associated with AAA include age, gender, family history, ethnicity, cholesterol, hypertension and smoking. One study demonstrated that men aged 65-70 years have a prevalence of 5.9%, increasing to 9.2% for those aged 76-80 years[12]. For women, a

prevalence of 0.5% was estimated in those aged 70 years[13]. The prevalence of AAA therefore increases with age and is lower in women than in men. Women do however appear to have a four-fold higher risk of aneurysm rupture[14].

Non modifiable

Genetics

A strong genetic component has been proven in the aetiology of AAA [15], however this remains as yet undefined. Those with a first-degree relative with AAA have between a 2- to 11-fold increased risk of developing an abdominal aneurysm themselves[16] and family and twin based studies indicate a heritability of approximately 70%[17]. This appears to be due to multiple small-effect genetic loci rather than a single gene defect. The first genome wide association study (GWAS) of AAA was published in 2009 and identified the association of a single-nucleotide polymorphism on Chromosome 3 with AAA (OR 1.33, P = 0.0028)[18] however these findings have not been replicated. Subsequently a much larger GWAS has identified LDL Receptor-related protein 1 as a biologically plausible genetic variant associated specifically with AAA and further studies are ongoing[16]. The genetics of AAA may in part explain some of the racial variation seen in the development of AAA for example Caucasian men[19] (prevalence 4.69%) are affected significantly more than Asian immigrants (0.45%) in the UK[20] and African Americans in the United States[21].

Modifiable

Cholesterol

Elevated blood cholesterol levels and hypertension have been repeatedly linked with the presence of AAA[22,23]. One meta-analysis found a significantly lower blood high density lipoprotein cholesterol level and significantly higher blood low density lipoprotein cholesterol level in patients with AAA compared to healthy controls[24]. Some studies have

suggested that treatment of high cholesterol with statins may reduce small aneurysm growth[25,26].

Hypertension

Another meta-analysis demonstrated that hypertension increased the risk of AAA[27], a finding which is supported by a study of individual patient data suggesting that hypertension is associated with an increase in AAA rupture rates[14].

Diabetes

Epidemiologic evidence suggests that patients with diabetes may have a lower prevalence of AAA, an observation which has been supported by a recent meta-analysis which demonstrated a significant inverse association between diabetes and AAA: pooled odds ratio 0.80; 95% confidence intervals 0.70-0.90 (P= 0.0009)[28]. This may in part be due to the effect of diabetes on AAA growth rates with one study[14] showing that growth rates decreased, by about a quarter in patients with diabetes but increased by about one-sixth in current smokers which also doubled the risk of aneurysm rupture.

Smoking

A recent Danish population based analysis suggested that tobacco smoking is the most important predictor of future hospitalization or death from aortic aneurysm in the Danish population and that approximately 50% of AAA cases would not have occurred had tobacco smoke exposure been absent[22]. Several prospective studies have demonstrated a dose-dependent relationship between the risk of AAA in smokers compared to non-smokers for example one study[21] suggested relative risks of 3, 5, and 7 for current smokers of less than 1 pack/day, between 1 and 2 packs/day, and of 3 or more packs/day respectively. Others have suggested that the duration of smoking rather than amount smoked has a more

significant effect on the risk of AAA formation and that the risk of AAA only gradually reduces over time after smoking cessation[29]. Smoking is the most consistent risk factor linked to the development of AAA thus current trends in the uptake of smoking tobacco are important to understanding future changes in AAA epidemiology. I will examine these trends in more detail in the next section.

1.3 Smoking trends throughout Europe

Smoking is the only modifiable risk factor that has been associated with the development, expansion[30,31] and rupture of AAA[32], and is therefore integral to AAA epidemiology and future trends in AAA related mortality. An overview of the current landscape of smoking in Europe is therefore informative in guiding the placing of future resources and the aim of this chapter is to describe and analyse current trends in smoking using internationally validated sources of European smoking data.

Christopher Columbus first brought tobacco leaves and seeds with him from the New World to Europe in the late 15th Century[33], however, it was not until the 16th Century that Jean Nicot de Villemain (after whom Nicotine was named) popularised tobacco in Europe. Cigarettes, which made use of scraps of tobacco by hand-rolling them in paper, were introduced in the 19th century and later became mass produced, fuelling a 20th century global epidemic responsible for 700,000 deaths annually in the European Union[34] and causing hundreds of billions of pounds of economic harm annually in the form of excess health-care costs and lost productivity[35].

A recent Danish population based analysis suggested that tobacco smoking is the most important predictor of future hospitalisation or death from AAA[22] and several prospective studies have demonstrated a dose-dependent relationship between the risk of AAA in smokers compared to non-smokers [21]. More than a decade has passed since the adoption of the first European tobacco products directive (2001/37/EC)[36], however, tobacco use remains high throughout Europe with an estimated 28% of adults in the European Union (approximately one hundred and twenty million people) currently smoking[37].

With the revision of the tobacco products directive formally approved by the European Parliament in February 2014, member states have 2 years to incorporate new changes into their national law. Not all European countries are however bound by these changes and in this section I will review differences in smoking prevalence and policy throughout Europe with the aim of informing future local smoking cessation practises for vascular surgeons.

Methods

Smoking data was extracted from the International Mortality and Smoking Statistics database (Version 4.09)[38] and the WHO Report on the Global Tobacco Epidemic, 2013[39]. Although differences exist in the types of tobacco products used in different countries and grown or manufactured in different regions of the world, data on cigarette smoking are among the most widely reported and are common to all countries[39]. The International Mortality and Smoking Statistics Database made estimates from data presented in international smoking statistics (ISS3)[40] for standardised age groups averaged by gender, 5 year period and 5 year age group. The data included into this study were gender specific prevalence of smoking (the percentage of the population who currently smoke cigarettes or any tobacco products). The definition of smokers used included those who smoke either cigarettes only or cigarettes and other products (pipe, cigars, etc.). This data was survey-based being derived from studies in which subjects are asked about their current smoking habits and were obtained from a variety of sources including nationally representative surveys or sources providing international comparisons. These estimates commonly start around the 1950's (range 1946-2010) and assume that there were no smokers below the age of 15. Only countries where gender specific data on smoking prevalence was available were included into this study.

The WHO Report on the Global Tobacco Epidemic[35] made estimates from nationally representative surveys based on the estimated prevalence of smoking among those aged fifteen years or more in the year 2011. This report provided information about tobacco-use prevalence, smoking prevention measures, smoking cessation and tobacco economics. Age standardised daily smoking prevalence was presented as both gender specific and total prevalence. Data were age standardised by the WHO to the WHO standard population to allow comparison between countries. Information regarding tobacco control measures and programmes were correct as of 31 December 2012 and data on tobacco taxation policy were correct as of 31 July 2012. Data regarding prices relate to the price of twenty of the most commonly sold brand of cigarettes in international dollars. An international dollar has the same purchasing power as the United States dollar has in the United States. Costs in local currency units are converted to international dollars using purchasing power parity (ppp) exchange rates.

A ppp exchange rate is the number of units of a country's currency required to buy the same amounts of goods and services in the domestic market as a U.S. dollar would buy in the United States. An international dollar is, therefore, a hypothetical standardised currency used to compare costs from one country to the other using a common reference point[36]. The ppp exchange rates used in this analysis were that used by WHO. Data regarding taxes on that brand are given as a percentage of the entire retail price. Smoking data was further analysed by longitude defined as the angular distance of any point on Earth measured east or west of the Greenwich meridian. All data relating to countries within the common definition of Europe and available data within the above databases were included.

Hospital Mortality data

Data regarding mortality were extracted from the European Health For All Database (HFA-DB) on 06/03/2014. The main data sources used in the HFA-DB are: health statistics in Member States (collected by The Health Information and Evidence Unit); WHO technical units and collaborating centres; and other international sources[41]. Ischaemic heart disease (I20-I25) mortality was age standardised using the direct method which represents what the mortality would have been if the population had the same age distribution as the standard European population. This was presented per 100,000 population.

Statistics

Data were analysed by standard linear regression where appropriate using SPSS v.22 (IBM Corp, Armonk, NY)

Results

Current smoking prevalence

Age standardised smoking prevalence varies across Europe (Table 1.1). For males the age standardised smoking prevalence varied from 13% in the United Kingdom (UK) to 59% in the Russian Federation. A smoking prevalence of under 20% was reported in the UK and Iceland whilst three countries reported a prevalence of over 50% including Belarus, Georgia and The Russian Federation. For females, age standardised smoking prevalence again varied from under 1% in Azerbaijan to 47% in Austria. Four countries reported a female smoking prevalence of less than 10% including Azerbaijan, Armenia, Georgia and Moldova. The highest smoking prevalence's in females (Bulgaria 31%, France 32%, Greece 34%) with the exception of Austria (47%) were lower than the highest smoking prevalence's for men (Ukraine 49%, Belarus 50%, Georgia 55%, Russian Federation 59%) suggesting that the overall prevalence of smoking in women remains lower than that for men.

Table 1.1 – The demographics of smoking in Europe

Country	Smoking Prevalence, Male (%)	Smoking Prevalence Female (%)	Price of pack of 20*	Taxes on this brand (% price)	Smoking cessation support
Ukraine	49	14	1.75	67	No
UK	13	14	9.79	80.1	Fully
Turkey	42	13	4.89	80.3	Partially
Switzerland	27	21	4.81	62.2	Partially
Sweden	25	24	5.6	73.8	Partially
Spain	33	27	5.56	79.3	Partially
Slovenia	28	21	4.56	80.1	Partially
Slovakia	39	19	4.82	83.9	Partially
Serbia	38	27	3	75.9	Fully
Russian Federation	59	25	1.85	40.5	No
Romania	38	18	6.11	73.2	No
Portugal	30	15	6.11	76	Fully
Poland	38	27	5.85	79.6	No
Norway	28	26	8.33	72.8	No
Netherlands	27	23	6.61	72.2	Fully
Montenegro	N/A	N/A	2.18	80.5	Fully
Moldova	43	5	1.8	43.7	No
Malta	31	20	7	76.9	Fully
Luxembourg	N/A	N/A	4.51	70.6	Partially
Lithuania	43	25	4.86	75.3	Partially
Latvia	46	20	4.42	79.1	No
Italy	31	18	5.84	75.2	No
Republic of Ireland	N/A	N/A	10.56	79	Partially
Iceland	19	18	7.42	57	N/A
Hungary	35	27	5.15	83.7	Fully
Greece	46	34	5.1	82.2	Partially
Germany	35	25	6.28	73	Partially
Georgia	55	3	1.37	58.1	N/A
France	39	32	6.78	79.9	Partially
Finland	27	23	4.98	79.9	Partially
Estonia	43	21	5.16	76.9	No
Denmark	30	27	4.61	79.3	Fully
Czech Republic	32	24	5.03	77.6	N/A
Cyprus	41	18	4.88	75.9	Fully
Croatia	36	30	4.63	71	Partially
Bulgaria	48	31	6.13	83.6	Partially
Bosnia and Herz	44	27	3.46	74.8	Partially

Belgium	31	23	5.83	76.1	Partially
Belarus	50	11	2.36	42.5	Partially
Azerbaijan	34	1	2	18.6	N/A
Austria	46	47	5.2	74.2	Partially
Armenia	47	2	2.69	25	N/A
Albania	48	5	3.22	60.7	N/A

- * international dollars, most sold brand in each respective country (2012)
- N/A = Not available

These data highlight some important differences between Western and Eastern European smoking prevalence. France, Spain, Belgium and the UK which represent the western most European countries (by longitude) reported male smoking prevalence's of 39%, 33%, 31% and 13% respectively. Armenia, Azerbaijan, Georgia and The Russian Federation, which represent those countries included with the eastern most longitude, had male smoking prevalence's of 47%, 34%, 55%, and 59% respectively. This suggests a higher prevalence of smoking in eastern European males (Figure 1.2). France, Spain, Belgium and the UK reported female smoking prevalence's of 32%, 27%, 23% and 14% respectively whilst Armenia, Azerbaijan, Georgia and the Russian Federation had smoking prevalence's of 2%, 1%, 3% and 25%. According to these data, Western European females have higher smoking prevalence's than their Eastern European counterparts (Figure 1.3). In almost all European countries (except Austria and the UK) the prevalence of smoking is higher in adult men than it is in adult women, however, the difference in prevalence of smoking between men and women is wider in Eastern Europe than in Western Europe. For example, in Armenia, over 50% of men smoke, compared to just 1.5% of women while in Spain 33% of men smoked compared to 27% of women.

Figure 1.2 – Male smoking prevalence across Europe (Ordered by longitude)

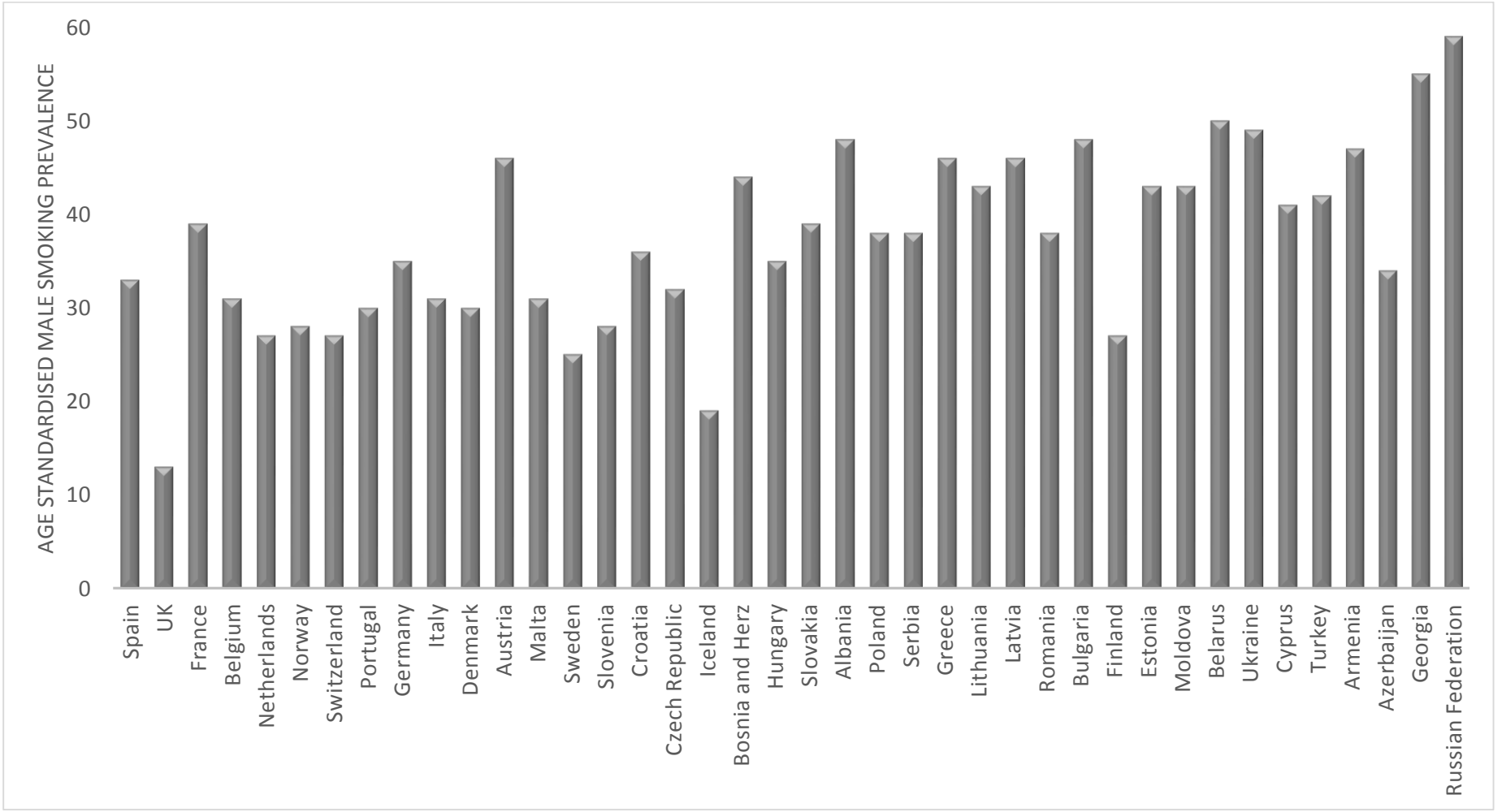
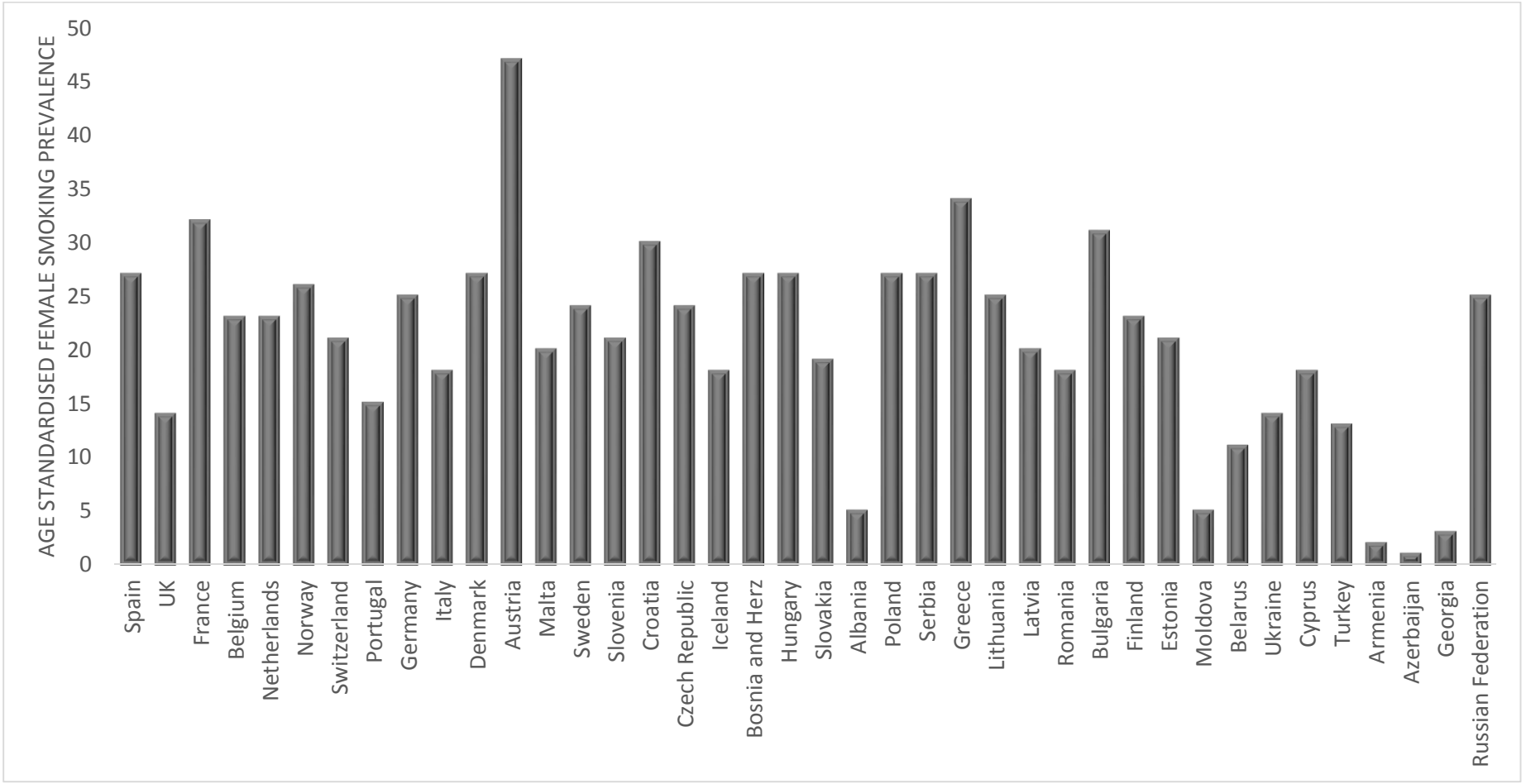


Figure 1.3 – Female smoking prevalence across Europe (Ordered by longitude)



Comparison of legislation

One approach to analysing why this variation exists is to compare the country with the lowest current overall smoking prevalence against the highest. The UK (overall smoking prevalence = 14%) signed up to the World Health Organisation Framework Convention on Tobacco Control in June 2003 and has since enforced smoke-free environments within healthcare facilities, educational facilities, government facilities, indoor offices, restaurants, cafés, pubs, bars, and on public transport. This legislation is backed up by fines on the establishment/smoker and additionally the UK National Health Service fully covers the cost of nicotine replacement therapy (NRT) and smoking cessation support. Comparatively, Austria (overall smoking prevalence = 46%) has enforced smoke free environments only in educational facilities (not including universities) and do not fully cover the cost of NRT or smoking cessation support on their health service. They did however, sign up to the World Health Organisation Framework Convention on Tobacco Control in August 2003.

The Russian Federation is not a signatory of the World Health Organisation Framework Convention on Tobacco Control and has the highest male smoking prevalence in Europe at 59%. Currently no legislation exists regarding smoke free environments and the Russian health service does not cover the cost of NRT or smoking cessation support. Both the UK and Austria have enforced bans on direct and indirect tobacco advertising, promotion and sponsorship. The Russian Federation has enforced direct bans on tobacco advertising via the television and radio, however, no legislation bans the advertising of tobacco products in magazines, newspapers, on billboards (or other outdoor advertising) or on the internet. Looking more widely, service provision in Europe to assist smoking cessation is generally poor and currently few countries (UK, Cyprus, Romania) fully cover the costs of smoking

cessation support and NRT. Furthermore, there are European nations where pharmacotherapy including nicotine replacement, bupropion (Zyban, Wellbutrin) and varenicline are not legally available. The early introduction of smoking cessation legislation in the UK may have contributed to a reduction in mortality from cardiovascular disease (Figure 1.4a/b) although other confounders exist for example the introduction of statins and percutaneous coronary interventions. Unfortunately historical data regarding AAA mortality is unavailable over such a long timescale however AAA has the same risk factors as ischaemic heart disease.

Taxation and cost

The price of the most commonly sold pack of twenty cigarettes in the UK is 9.79 international dollars from which 80% of the price is made up of taxes including specific excise, ad valorem excise and value added tax. Comparatively in Austria and The Russian Federation the price of the most commonly sold pack of twenty cigarettes is 5.20 (74% tax) and 1.85 (40.5% tax) international dollars respectively therefore vast differences exist. Analysing the association between cigarette pricing and smoking prevalence (Figure 1.5a/b) demonstrates an association in males, however, for reasons that are unclear, this association does not appear to be as well defined in females. These data also highlight differences in pricing between Western and Eastern Europe (Figure 1.6).

Figure 1.4a, Smoking cessation legislation in the United Kingdom and age standardised mortality from ischaemic heart disease

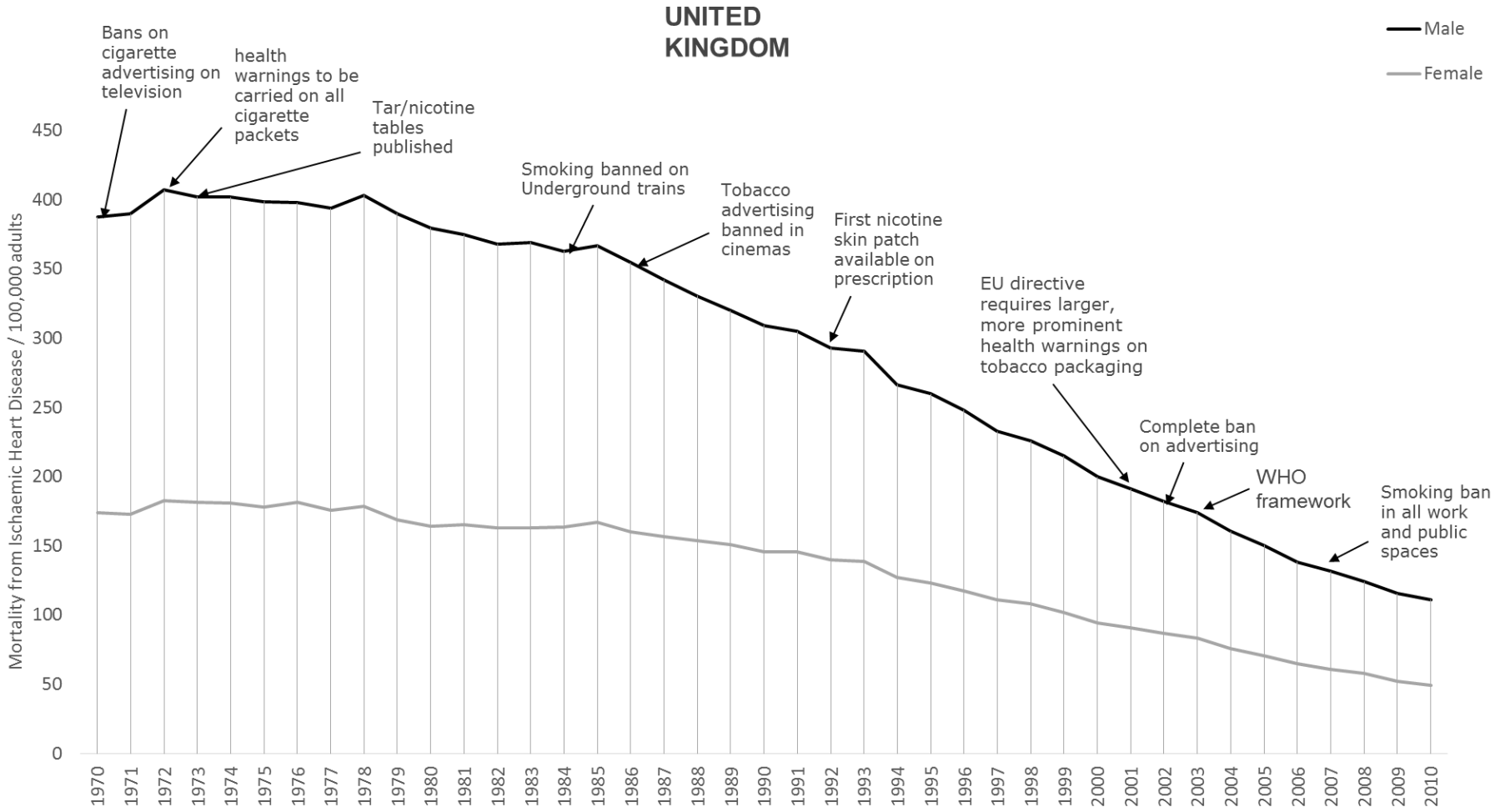


Figure 1.4b, Smoking cessation legislation in Romania and age standardised mortality from ischaemic heart disease

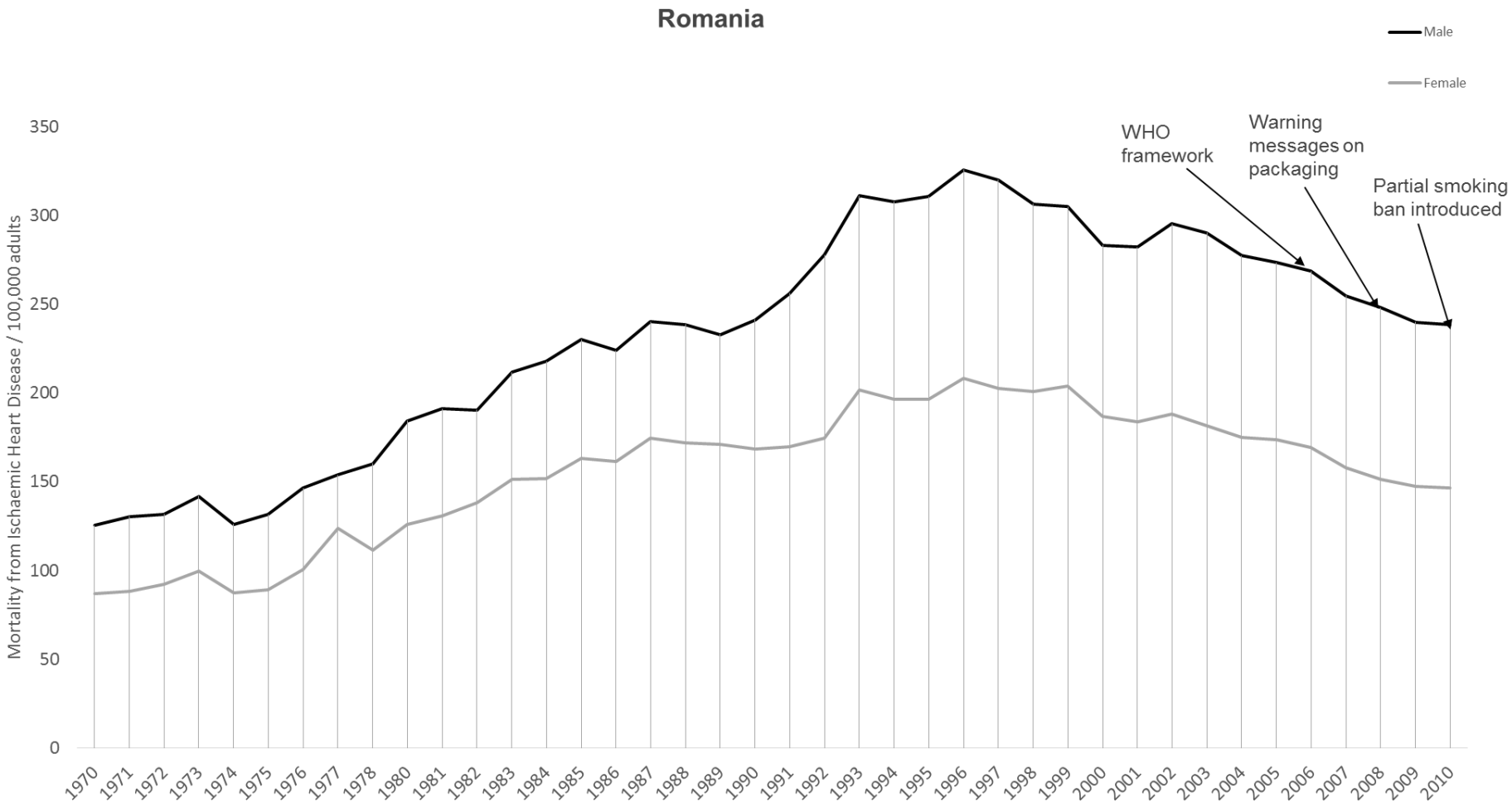


Figure 1.5a – The association of cigarette pricing and male smoking prevalence, each dot represents a country

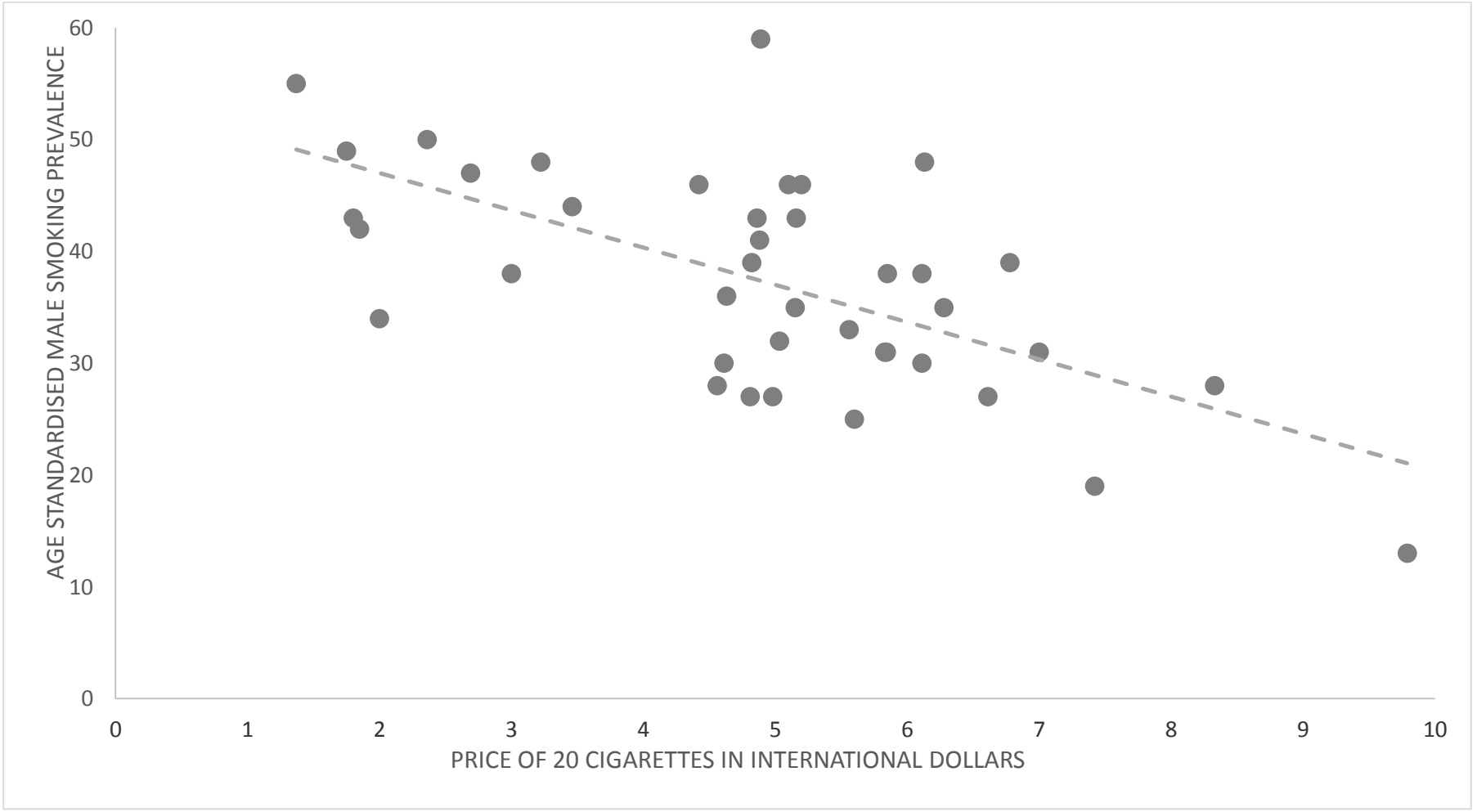


Figure 1.5b– The association of cigarette pricing and female smoking prevalence, each dot represents a country

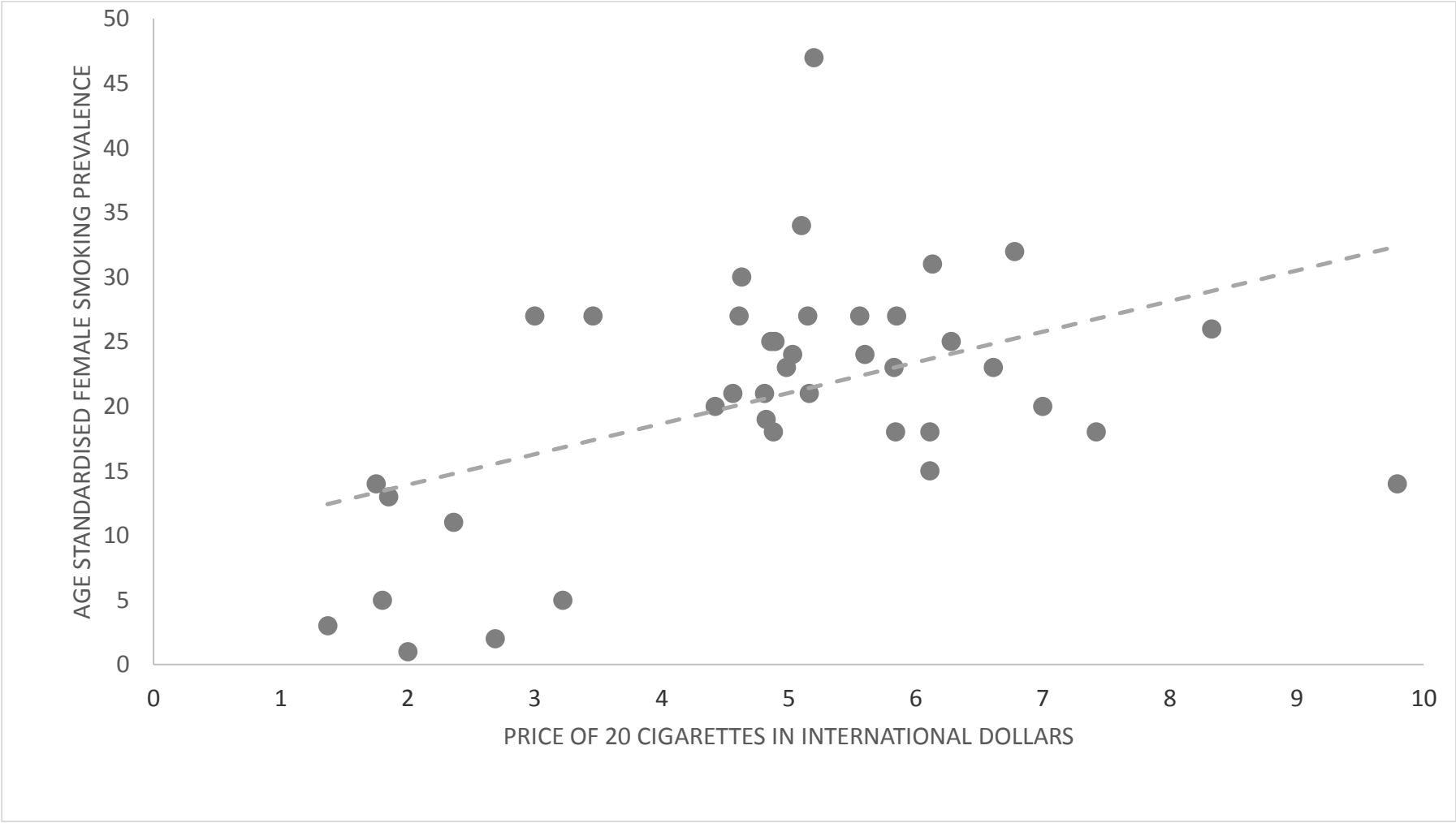
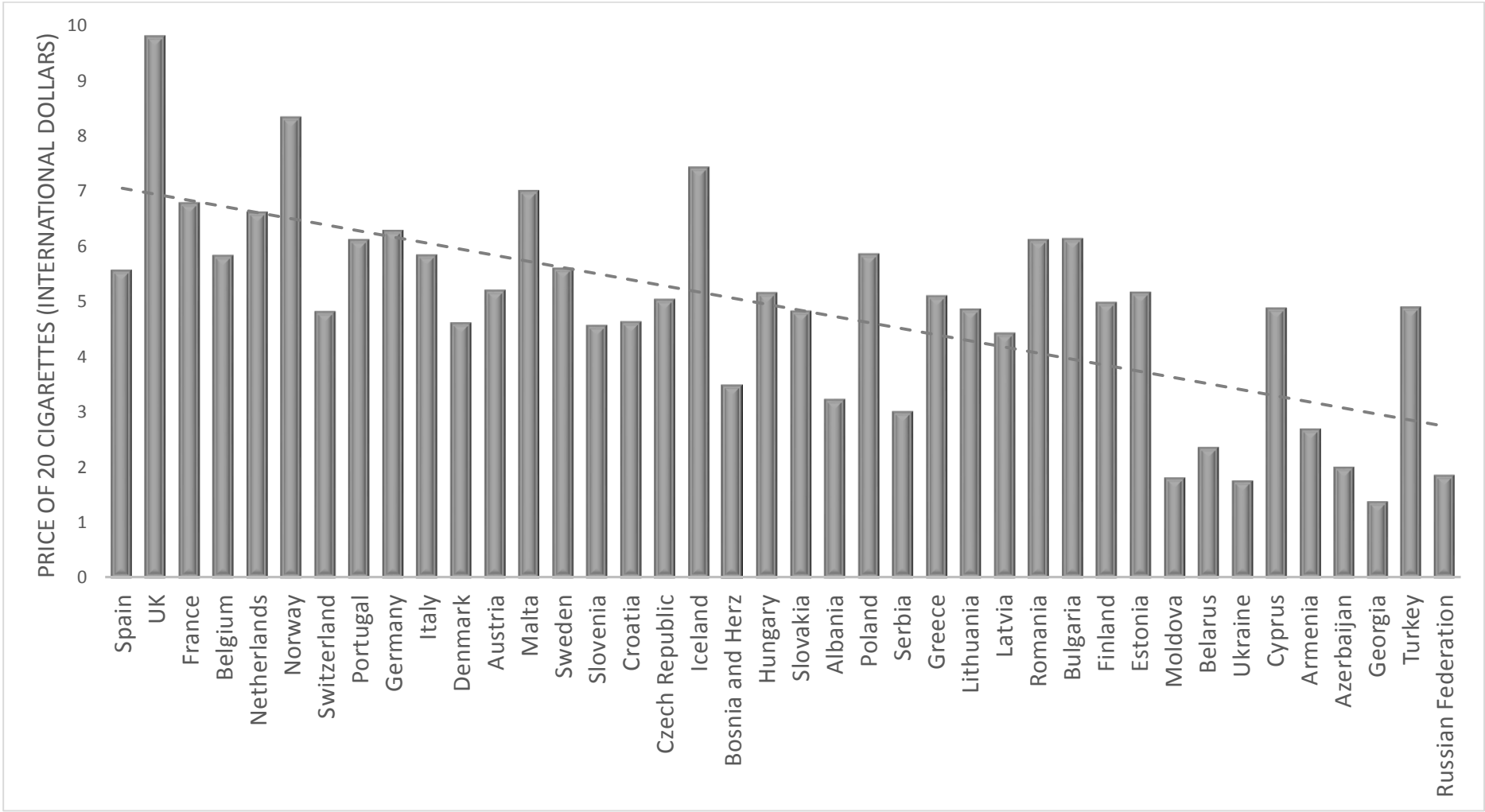


Figure 1.6 – Differences in pricing of cigarettes across Europe with trend line (Ordered by longitude)



Discussion

Smoking prevalence throughout Europe displays a large amount of variability with vast differences between Western and Eastern Europe. Eastern European countries continue to report high smoking prevalence rates in men whilst smoking prevalence is lower in Eastern European females. Smoking prevalence remains generally lower among females compared to males. Vast variations exist in smoking cessation policies throughout Europe and these likely contribute to low smoking cessation rates in some countries. On a national and international scale, more could be done to reduce cigarette smoking and the excess morbidity and mortality associated with its use.

Several mechanisms exist by which smoking may have its effects and the over 4,000 compounds[33] found in tobacco smoke likely play a role. Although the precise role of smoking in the development of cardiovascular disease has yet to be established, its effect on vascular endothelial function, atherosclerosis and thrombus development make smoking cessation an important intervention. A systematic review of prospective cohort studies[42] including patients diagnosed with coronary heart disease (CHD) suggested that smoking cessation is associated with a substantial reduction in risk of all-cause mortality and importantly that this risk appears to be reduced more through smoking cessation than through standard cardiovascular treatments including the use of antiplatelet, antihypertensive's and statins[43]. The focus of a clinical encounter may therefore be better placed on appropriate smoking cessation support then simply on prescriptions as smoking cessation is both clinically and cost effective[44].

Smoking policy has a well-established role in reducing smoking prevalence[45,46], however, it varies considerably between countries. Smoking cessation rates remain low with a high annual relapse rate in those who do attempt to quit. Many smokers cite the advice of physicians as a key motivation to quit, yet there is widespread evidence that healthcare professionals are failing to address the smoking habits of their patients[47] and that few smokers successfully quit without help[48]. One approach to improving smoking cessation rates would be for clinicians to ask and address the smoking habits of their own patients. Counselling of just 3 minutes has been estimated to increase the odds of quitting by 1.3 relative to no counselling[49]. This is something that could be achieved within the timeframe of a vascular surgical clinic or during surveillance in patients diagnosed with a small AAA.

An understanding of local guidelines and available options is vital for example behavioural therapies alone have been shown to approximately double, and together with pharmacotherapy, quadruple, the likelihood of successful quitting[45]. All vascular surgeons should be familiar with local smoking cessation support as the prevalence of smoking among vascular surgical patients is widely recognised to be high. Furthermore, recent evidence suggests that smoking cessation advice is more likely to be successful in smokers with a diagnosed AAA compared to those without[50]. It is unclear why there are differences between male and female smoking prevalence. It is plausible that historical smoking cessation strategies were primarily aimed at males and some current marketing strategies specifically aimed at women exist. Female smoking prevalence has increased in many countries as a result of this direct marketing, causing an increase in smoking related cancers[51]. This may also result in an increase in the number of females developing AAA.

The revised Tobacco Products Directive which will first be applied in 2016 recommends that 65% of a cigarette pack should be covered in health warnings (front and back); introduces a new robust system of reporting ingredients including a ban on additives claimed to enhance energy or vitality (such as caffeine and taurine); and ensures that standardised pack sizes should hold no less than 20 cigarettes so that they are less affordable for young people. A wide variation exists in the implementation of national smoking cessation policies and by addressing these national inequalities, the substantial harm caused by tobacco use could be reduced. By playing a proactive role in local smoking cessation strategies, vascular surgeons could improve their patients' health, and potentially the results of any interventions performed.

Summary

1. **Male smoking prevalence is higher in eastern Europe**
2. **Female Smoking prevalence is higher in western Europe**
3. **Vast variations exist in smoking cessation policies throughout Europe.**

Chapter 2: The Aneurysm Global Epidemiology Study

2.1 A population study of abdominal aortic aneurysm mortality

In the 20th century, AAA was a disease on the rise, with evidence of a steady increase in aneurysm prevalence and mortality in the United Kingdom (UK)[52] and the United States of America (USA)[53]. This triggered randomised trials of ultrasound screening of AAA in an effort to address the AAA epidemic, which revealed the benefit of screening in reducing deaths from AAA related mortality[54,55]. However, contemporary data from western populations[56] have reported a reversal in AAA epidemiology, with steep declines in AAA prevalence and mortality during the 21st Century. The cause of this decline is currently unknown and is the focus of this chapter.

It is possible that these observations are secondary to population level temporal changes in known risk factors for AAA for example levels of high cholesterol, hypertension, diabetes and smoking. As described earlier, smoking is the only modifiable risk factor that has been associated with the development, expansion[30,31] and rupture of AAA[32] with a causative link recently being revealed *in vivo* within a mouse model[57]. A decline in smoking is likely to have contributed significantly to the current reversal of the AAA epidemic[58] however this trend is not the same across the world where recent decades have seen a massive expansion in tobacco use and accelerating growth in smoking among women in the developed world[59].

Variation between countries has also been noted for cholesterol levels and the prevalence of hypertension. For example, a recent population based systematic analysis of worldwide mean total cholesterol levels[60] highlighted differences in cholesterol levels between genders and demonstrated opposite trends in Australasia, North America, and Europe, where serum

total cholesterol decreased from previously high concentrations, and East/Southeast Asia and the Pacific, where it rose from low concentrations. Another population based analysis[61] of health and epidemiological studies revealed that high income regions (males and females in Western Europe) had the highest mean systolic blood pressures.

Global trends in AAA mortality are currently unclear and variations in trends of its main modifiable risk factors will provide a valuable opportunity to investigate underlying factors associated with the disease. I hypothesise that the decline in mortality seen in some developed countries is not being seen globally and that associations exists with risk factor exposure. This study aims to examine global trends in AAA mortality and investigate the link between smoking and other common cardiovascular risk factors with AAA mortality.

Methods

Identification of AAA mortality rates

Age, gender and cause specific mortality are made available by the World Health Organisation for all member states (all countries which are Members of the United Nations may become members of WHO by accepting its Constitution) who classify cause of death according to the International Classification of Diseases, 10th Revision (ICD-10). Information relating to the ICD-10 codes I71.3, I71.4, I71.5, I71.6, I71.8, and I71.9 which represent abdominal and thoracoabdominal aortic aneurysms, ruptured or otherwise, and aortic aneurysms of unspecified site (ruptured or otherwise) were extracted on 01/08/2012. Thoracoabdominal aortic aneurysms and aneurysms of unspecified site were included within this analysis to ensure that all lesions involving AAA were captured in the analyses. No age restrictions were placed and all available data was extracted for analysis. The availability of mortality data for each year varied between countries (range 1994-2010) however the WHO

mortality database is the largest validated international mortality dataset and these differences have been taken into account within the analysis. ICD-10 codes are generated through civil registration systems which are a major source of cause of death data recorded by the World Health Organisation (WHO)[7] and only WHO member states with a data completeness rate of 70-100% were included into the study[62] (Table 1.2)

Table 1.2, table of quality of cause of death statistics reproduced with permission from Mahapatra et al[35].

Quality of cause-of-death statistics reported to the WHO	Countries
High quality 90–100%	Austria, Australia, Bahamas, Canada, Chile, Cuba, Costa Rica, Estonia, Finland, Hungary, Iceland, Ireland, Israel, Japan, Kuwait, Latvia, Lithuania, New Zealand, Malta, Mexico, Moldova, Romania, Saint Vincent and the Grenadines, Singapore, Slovakia, Sweden, Trinidad and Tobago, USA, UK, Venezuela , Uzbekistan.
Medium high quality 70–100%	Antigua and Barbuda, Barbados, Belize, Belgium, Croatia, Colombia, Czech Republic, Denmark, Dominica, Former Yugoslav Republic of Macedonia Georgia, Germany, Italy, Kyrgyzstan, Netherlands, Niue, Norway, Mauritius, Panama, Philippines, Slovenia, South Korea, Spain, Switzerland.
Medium low quality 70–100%	Belarus, Belarus, Bosnia and Herzegovina, Brazil, Brunei, Bulgaria, Cook Islands, Ecuador, France, Grenada, Guatemala, Kazakhstan, Luxembourg, Mongolia, Oman, Portugal, Russia, Saint Lucia, Seychelles, Saint Kitts and Nevis, San Marino, Serbia and Montenegro, Suriname, Turkmenistan, Ukraine, Uruguay.

Completeness of statistics on cause of death was defined as the ratio of number of deaths for which cause of death is registered to the civil registration system to the estimated total number of deaths in the population. Mortality data was converted into deaths per 100,000 of the population after which age-standardized rates of mortality (ASM) were calculated by use of the United Nations, department of economic and social affairs, world population prospects (2010) standard 'more developed regions' population[63]. This standard population reflects the average male and female age structure of regions including Europe, Northern America, Australia/New Zealand and Japan expected from 1950-2010

Smoking data

Smoking data was extracted from the International Mortality and Smoking Statistics database (IMASS Version 4.09)[38] which made estimates from data presented in international smoking statistics (ISS3)[40] for standardised age groups averaged by gender, 5 year period and 5 year age group. The data included into this study were gender specific prevalence of smoking (the percentage of the population who currently smoke cigarettes or any tobacco products). The definition of smokers used included those who smoke either cigarettes only or cigarettes and other products (pipe, cigars, etc.). No attempt was made to include data on smokers of hand-rolled cigarettes only or by type of manufactured cigarette (e.g. filter/plain, high/low tar, dark/blond tobacco).

This data was survey-based being derived from studies in which subjects are asked about their current smoking habits and were obtained from a variety of sources including nationally representative surveys or sources providing international comparisons. These estimates commonly start around the 1950's (range 1946-2010) and assume that there were no smokers below the age of 15. Only countries where gender specific data on smoking

prevalence was available were included into this study. ISS3 is the largest validated international smoking statistics dataset available and these differences have been taken into account within the analysis.

Risk factor data

Age standardised (male and female) mean total cholesterol (mmol/l), mean fasting blood glucose (mmol/l), mean body mass index (kg/m^2) were extracted for the years 1980-2010 whilst data on mean systolic blood pressure (mmHg) were extracted for the years 1995-2010 from the WHO InfoBase[63] on 01/09/2012. Systolic blood pressure (SBP) was analysed, rather than diastolic blood pressure (DBP), because prospective studies strongly suggest that SBP is a better predictor of cardiovascular disease risk[64], especially in older adults (≥55 years), in whom most deaths from cardiovascular disease occur. The WHO InfoBase reports country derived data from; Ministry of Health national estimates; National Health Surveys; Demographic and Health Surveys (DHS); Household surveys from other UN organizations; WHO-sponsored survey instruments and external research.

Countries included

After exclusion of countries based on completeness of statistics and availability of risk factor data the following 19 countries were included into this study: Australia, Austria, Canada, Denmark, Finland, France, Germany, Hungary, Iceland, Israel, Japan, Netherlands, New Zealand, Norway, Romania, Spain, Sweden, UK and USA (Figure 2.1a/b).

Figure 2.1a – Flow Diagram of included countries

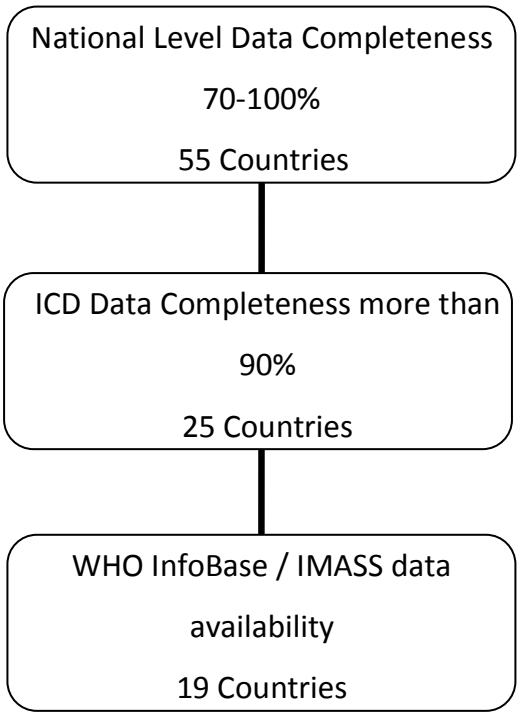


Figure 2.1b, Key for included countries

- Australia – Aus
- France - Fra
- Japan - Jap
- Spain - Spa
- Austria – Aut
- Germany - Ger
- Netherlands – Net
- Sweden - Swe
- Canada – Can
- Hungary - hun
- New Zealand- NZ
- United Kingdom - UK
- Denmark – Den
- Iceland - Ice
- Norway - Nor
- United States of America - USA
- Finland - Fin
- Israel - Isr
- Romania - Rom

Statistics

Men and women were analysed separately. Risk factor data including mean total cholesterol, mean fasting blood glucose, mean body mass index, mean systolic blood pressure and prevalence of smoking were plotted over all available time points from which slopes of the regression lines of the variable against time were calculated with standard errors. Similarly ASM was plotted over all available time points from which slopes of the regression lines against time were calculated with standard errors. Therefore, for each country trends in each respective risk factor for example blood cholesterol levels and trends in mortality were calculated and plotted together. The standard errors of variables such as the rate of change in smoking prevalence with time were calculated separately from the data for each country and then those standard errors were treated as known when fitting the regression model, as previously published by Deming[65].

The data were analysed by a linear errors-in-variables regression, a model which allows for uncertainty in both the response and explanatory variables namely; AAA mortality and the respective risk factor. The analysis was done this way because both x and y represent quantities estimated from annual civil registry data reported by each country. For example, x might be the annual increase or decrease in average blood pressure over a given time interval. These quantities are likely estimated with error and for each country we have both an estimate of x and of its standard error and similarly we have an estimate of y and its standard error. This differs from a standard linear regression model of y on x within which it is implicit that x is measured without error[66]. The model was fitted by maximum likelihood in Stata12 (StataCorp, TX) using the maximum likelihood command. The models were compared in a likelihood ratio test.

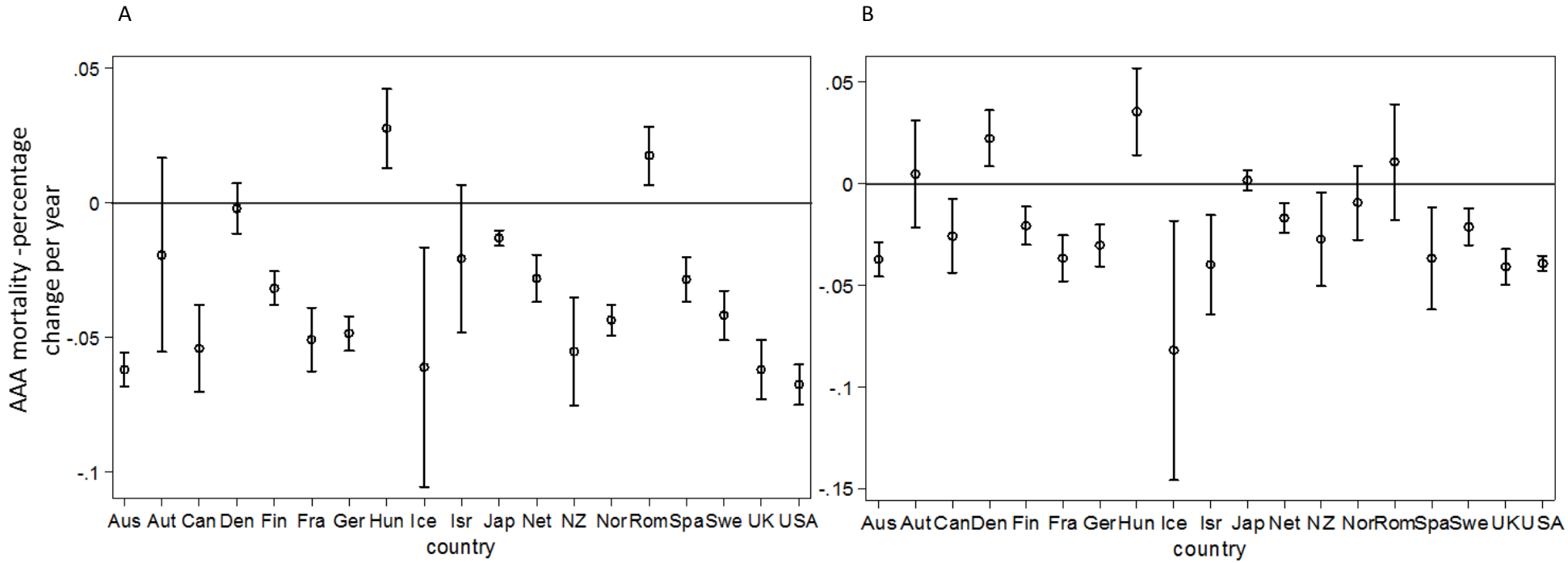
A further analysis was performed for each country by calculating total unadjusted (male and female) AAA deaths per year and comparing between two age groups for each country; Deaths due to AAA in individuals under 75 years of age and deaths due to AAA in those 75 years of age and over. The proportion of deaths in the two age groups and the change in these proportions over time was calculated for each individual country.

Results

Trends in AAA mortality

This study reveals substantial heterogeneity in AAA ASM trends globally although male and female AAA mortality appears to be declining in most populations (Figure 2.2a and 2.2b). The USA, UK and Australia appear to have the fastest declining male AAA ASM at 6.7%, 6.2% and 6.2% per year respectively. The largest reductions in female AAA mortality were seen in the UK and USA at 4% and 3.9% per year respectively therefore, it appears that the rate of decline in female AAA mortality is less than for male. Importantly AAA mortality is not declining globally as evidenced by an increase in male AAA ASM in Hungary (2.7%) and Romania (1.7%) and in female AAA ASM in Hungary (3.5%), Romania (1%), Denmark (2.2%) and Austria (0.5%). Some countries appear to have a declining AAA mortality in males and an increasing AAA mortality in females for example Denmark and Austria.

Figure 2.2, Trends in male (a) and female (b) age standardised AAA mortality with standard errors



Although mortality is decreasing in both the over and under 75 age groups, the percentage decrease appears to be greatest in the <75 age group. In the UK <75 mortality decreased from 30% in 2001 to 24% in 2009 (-0.8% per year) however the largest decline in the <75 group was seen in Japan (-0.9% per year). In total 14/19 countries had a decrease in <75 mortality while 16/19 countries saw increases in mortality in the >75 age group. Only the Netherlands appeared to have an increasing mortality trend in the <75 age group from 36% in 2001 to 43% in 2009 (1.3% increase per year).

Trends in risk factors

Temporal trends in the common cardiovascular risk factors show a significant amount of heterogeneity across the countries studied. Male trends in BMI (1980-2008) ranged from +0.1 kg/m^2/year observed in the USA to +0.02 kg/m^2/year in Romania whilst female BMI trends ranged from 0.12 kg/m^2/year to -0.01 kg/m^2/year again with the largest increase seen in the USA and the smallest change observed in Romania. Trends in male mean total cholesterol (1980-2008) ranged from +0.02mmmol/l/year in Japan to -0.03mmol/l/year seen in Finland while trends in female total cholesterol ranged from +0.01mmol/l/year to -0.04mmol/l/year in Japan and Sweden respectively.

Trends in mean fasting blood glucose (FBG) varied significantly between countries, ranging in males from +0.02mmol/l/year in Spain to -0.003mmol/l/year in the Netherlands while female mean FBG ranged from 0.02mmol/l/year to -0.01mmol/l/year again in Spain and the Netherlands respectively. Trends in male mean systolic blood pressure (1995-2008) ranged from -0.41mmHg/year seen in the UK to -0.02mmHg/year in Spain whilst mean female systolic blood pressure ranged from -0.57mmHg/year again

in the UK to -0.14mmHg/year seen in Romania. Smoking prevalence varied considerably between countries and gender with male smoking prevalence declining in most countries whilst female smoking prevalence was increasing in 6 out of 19 the countries reviewed. The largest reduction in male smoking prevalence was seen in the Canada (-4.1% per year) and Spain (-3.4% per year) whilst the smallest reduction was seen in Hungary (-1.3% per year). Only one country was seen to have an increasing male smoking trend (Romania, +0.6% per year). The largest increases in female smoking prevalence were seen in Spain and Romania at +1.4% and +1.5 per year each whilst the largest decline was seen in Iceland (-3.5% per year).

The association of trends in AAA mortality to trends in risk factors

Regression analysis suggests that trends in systolic blood pressure (Figure 2.3a, P=0.028), cholesterol (Figure 2.4a, P=0.0082) and smoking prevalence (Figure 2.5a, P=0.017) are positively and significantly associated with changes in male AAA mortality while trends in BMI (Figure 2.6a P=0.0072) are negatively and significantly associated with changes in male AAA mortality. Similarly in females, trends in systolic blood pressure (Figure 2.3b, P=0.024), cholesterol (Figure 2.4b, P=0.024) and smoking prevalence (Figure 2.5b, P=0.00021) were positively and significantly associated with AAA mortality whilst trends in BMI were negatively and significantly associated with AAA mortality (Figure 2.6b, P=0.0039). The direction of the AAA mortality trend was in both males and females most similar to trends in smoking prevalence. AAA mortality was not found to be significantly associated with trends in mean FBG in males (Figure 2.7a, P= 0.306) or females (Figure 2.7b, P= 0.9).

Figure 2.3 - Linear regression revealing the positive association between temporal trends in male (a) and female (b) mean systolic blood pressure and AAA mortality.

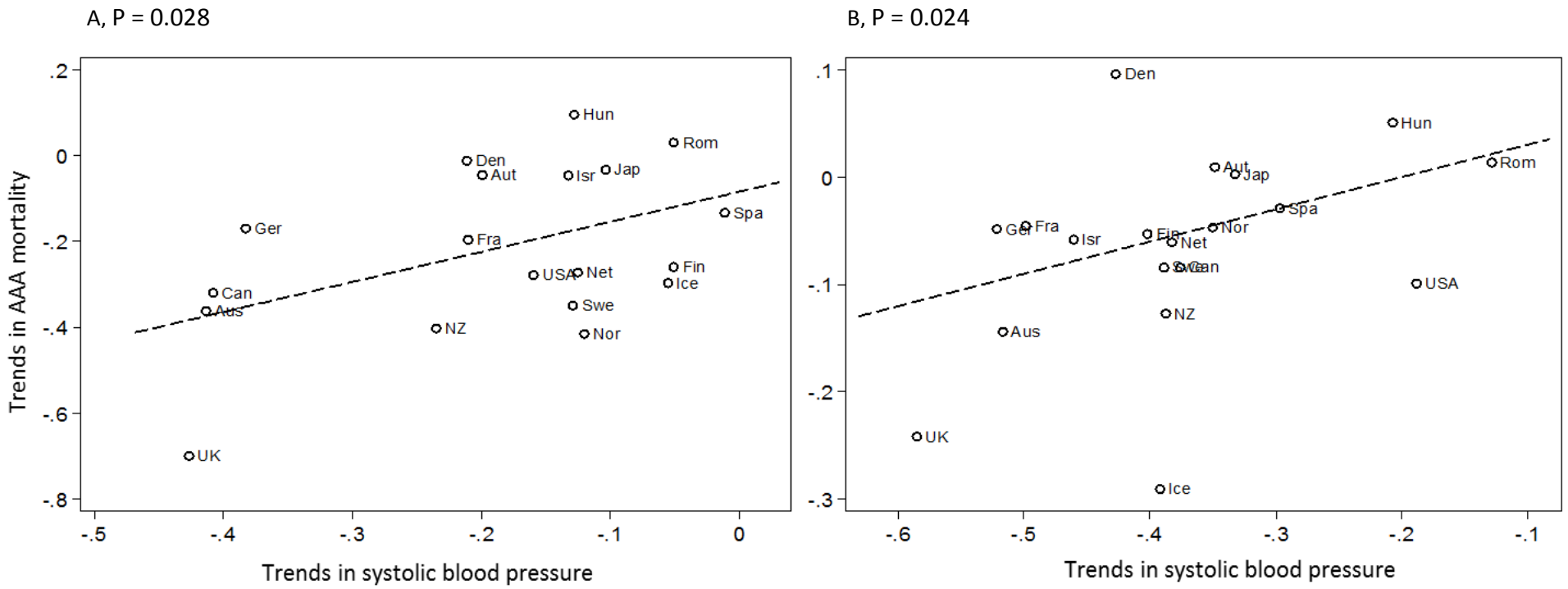


Figure 2.4 - Linear regression revealing the positive association between temporal trends in male (a) and female (b) mean total cholesterol and AAA mortality.

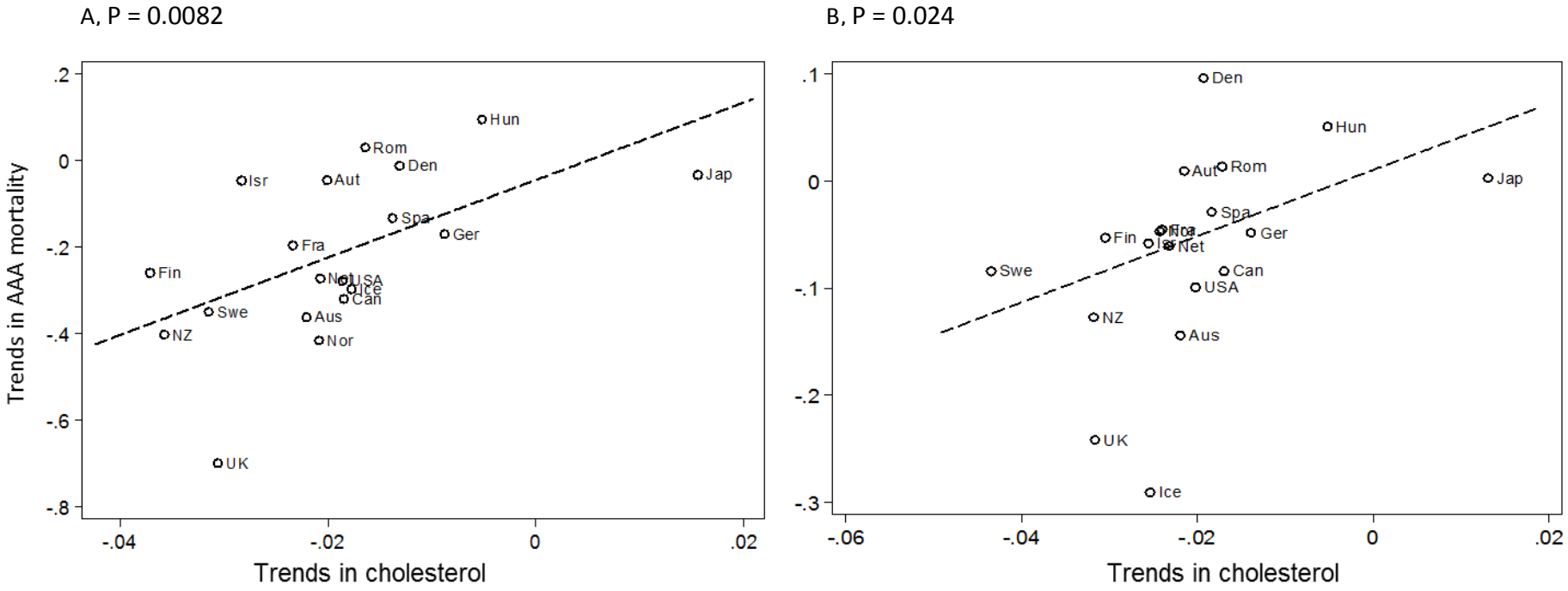


Figure 2.5 - Linear regression revealing the positive association between temporal trends in male (a) and female (b) smoking prevalence and AAA mortality.

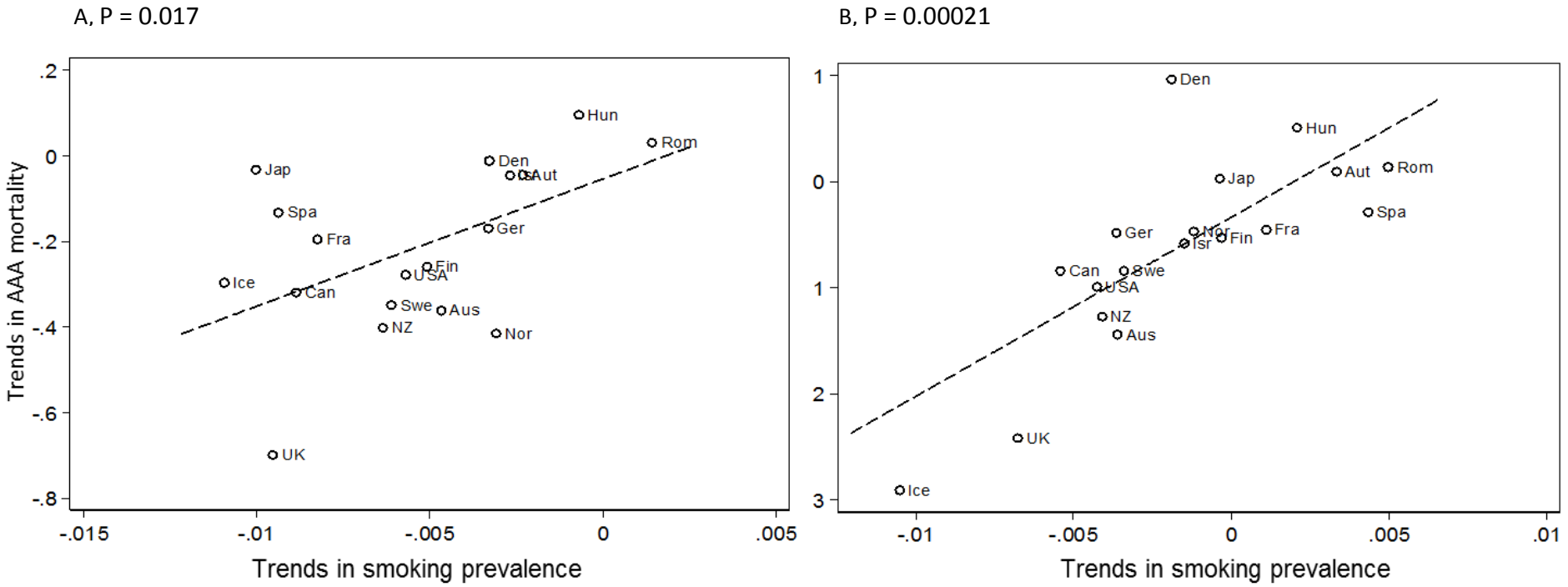


Figure 2.6 - Linear regression revealing the negative association between temporal trends in male (a) and female (b) mean body mass index and AAA mortality.

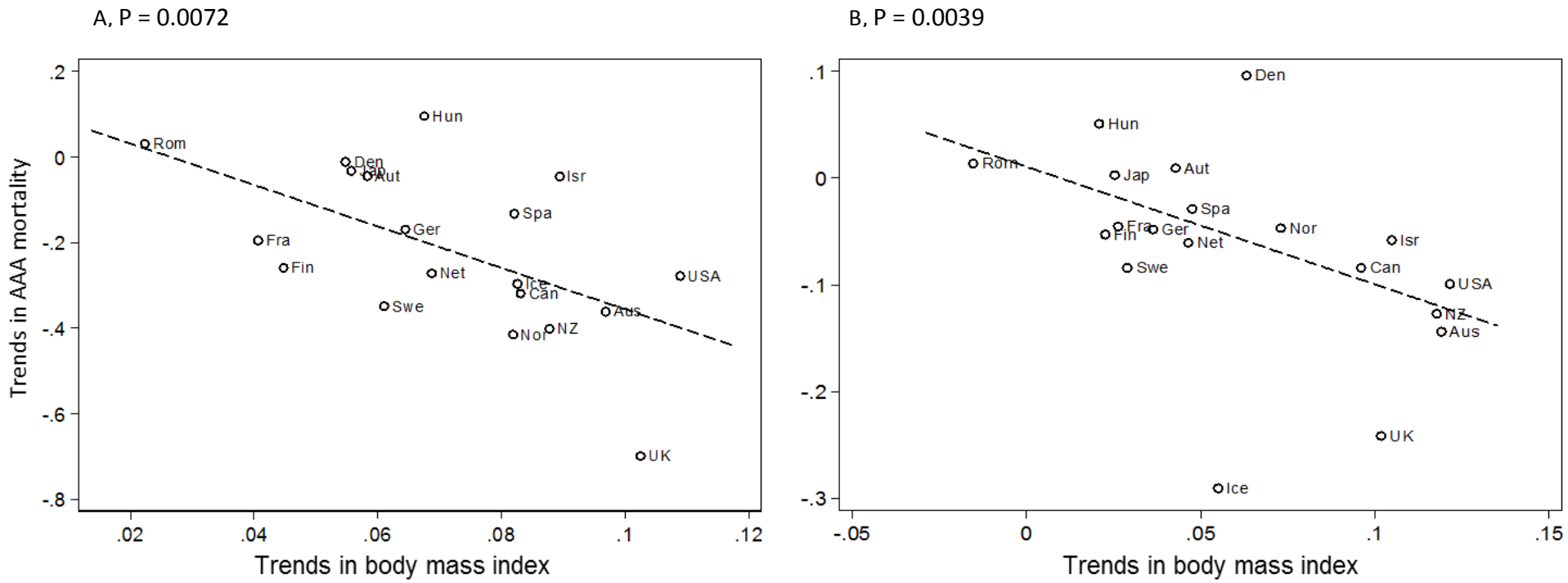
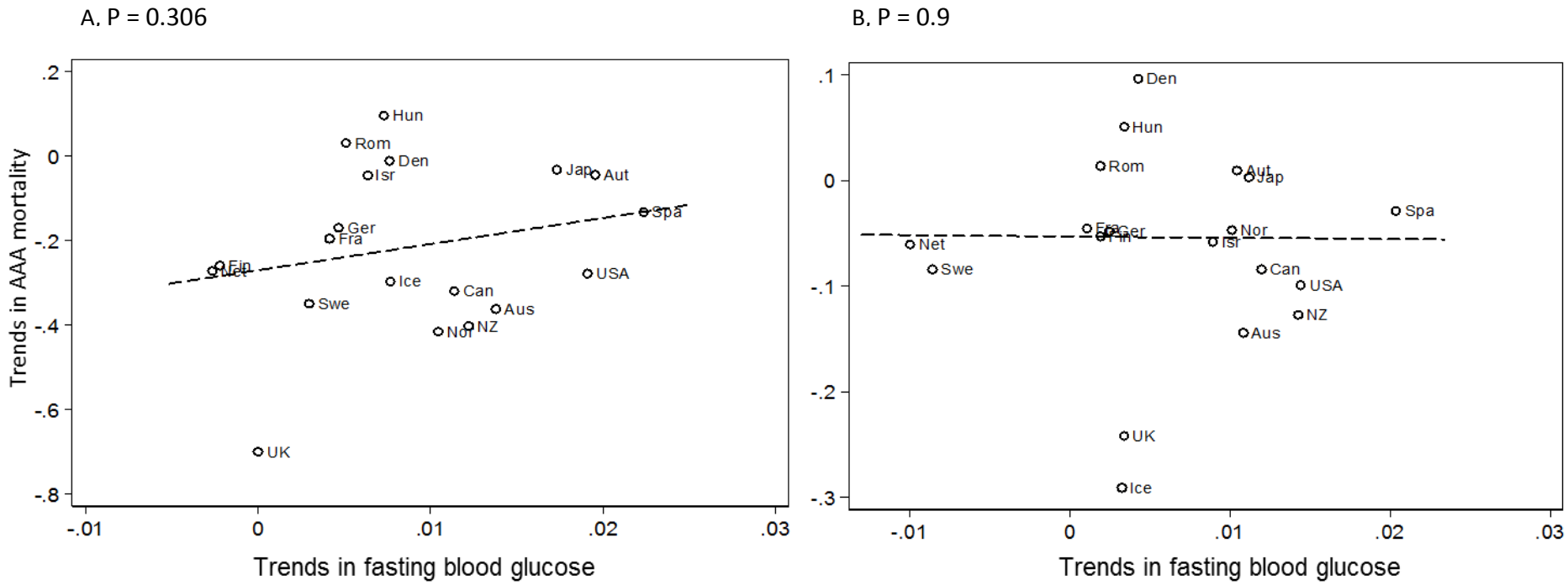


Figure 2.7, Linear regression revealing no association between temporal trends in male (a) and female (b) fasting blood glucose and AAA mortality.



Discussion

Between 1951 and 1995 epidemiological studies revealed that AAA was a disease on the rise, with a steady increase in aneurysm prevalence and mortality in the UK[52] and USA[53]. However, more recently, evidence from a number of countries suggests that [56,67] during the 21st century a reversal in AAA epidemiology has occurred, with steep declines in AAA prevalence and mortality. This study represents the largest population based analysis of AAA mortality to date and confirms that AAA mortality is declining in most developed economies; however that decline is not equal between countries, gender or age groups. In addition this is the first large population based study to demonstrate a relationship between global variations in common cardiovascular risk factors and AAA mortality suggesting that public health measures to reduce the prevalence of hypertension, high cholesterol and smoking could reduce global AAA mortality further.

Male and female AAA mortality is generally declining however the rate of decline is not equal with the UK and USA appearing to show the steepest drop in AAA mortality (male and female) whilst Romania and Hungary both show increases in AAA mortality across both genders. Male AAA mortality appears to be declining more sharply than female although in some countries an increasing trend in female AAA mortality has been seen with the reverse in males. This finding may reflect differences in risk factor exposure for example smoking trends are not the same across the world where recent decades have seen a general decline in male tobacco use with an accelerating growth of smoking among women in the developed world[59]. Tobacco use is the single most important preventable health risk in the developed world, with well-established links to the development, expansion and rupture of AAA[30-32] likely orchestrated by nicotine as evidenced by the findings of recent *in vivo* mouse model

studies[57]. This study demonstrates a strongly linear relationship between temporal trends in smoking prevalence and AAA mortality.

It is known that sexual dimorphism exists amongst a number of cardiovascular diseases[68], therefore it is possible that the pathophysiology of AAA development is different in females who have been noted to have a fourfold higher rupture rate[69] compared to males. In addition to the observed differences between genders, the percentage decline in AAA mortality appears to be more profound in the under 75 age group. This finding has previously been shown in the UK[67] which in addition to an observed increase in the number of elective admissions for AAA in the > 75 age group may suggest that improvements in public health do not prevent AAA but instead slow down the development of AAA in genetically predisposed individuals.

The finding that an elevated BMI may be independently associated with a decrease in AAA mortality is novel however it needs to be interpreted with caution. The association between traditional cardiovascular risk factors and an improvement in clinical outcomes has been observed in those with heart failure and chronic obstructive lung disease[70-72] with this association referred to as 'reverse epidemiology' or more recently the 'obesity paradox', however, whether a raised BMI actually confers any survival advantage on patients with AAA remains to be proven. Sweeting *et al*[69] revealed that an increased BMI was associated with a slower rate of AAA growth, however, this affect was lost after adjustment for demographics including medical history and drug history. A recent population-based cohort study[73] revealed waist circumference was positively associated with the risk of AAA however BMI was not. BMI is thought to reflect total adiposity, whereas waist circumference is an approximate index of intra-abdominal fat mass, which corresponds well to visceral adiposity

therefore it may be that visceral adiposity rather than total adiposity is important in the development of AAA. Smoking cessation has long been linked with weight gain[74] therefore one possible explanation for the obesity paradox is that countries with the greatest reduction in smoking prevalence may have increases in obesity but a decline in AAA mortality.

Whilst the association between obesity and AAA is unclear, epidemiological studies have demonstrated obesity as an independent risk factor for type II diabetes[75] and studies thus far appear to suggest a protective role for diabetes on the development of AAA[69,76] which may explain this observation. This study found no significant association between global trends in fasting glucose concentrations and AAA mortality which may suggest that the protective effect of diabetes is not secondary to changes in fasting glucose concentrations however this requires further investigation. One explanation for the lack of any association between AAA mortality and fasting glucose may be counteraction, with an increased mortality post AAA repair in diabetics[77] concealing any benefit gained from slower AAA development however, whether diabetes confers any survival disadvantage on patients post AAA repair is currently unclear[78]. Obesity is more common in economically developed countries therefore economic factors such as health expenditure could account for some of the differences observed in this study and it is of interest to note that the UK spent 9.3% of its gross domestic product on health expenditure in 2011 whilst the USA, Romania and Hungary spent 17.9%, 5.8% and 7.7% respectively[79].

Our results do not exclude the possibility of other factors influencing population trends in AAA mortality for example the exponential increase in prescriptions of antihypertensive and lipid lowering medication or the epidemic of type II diabetes effecting most developed

economies, however, these effects are taken into account in that they effect population distributions of each relevant risk factor. Changes in the treatment of AAA have occurred during the study period for example, since the introduction of endovascular aneurysm repair (EVAR), it has become established as the treatment of choice for most suitable patients in many vascular centres. However a recent meta-analysis[80] revealed no long-term survival benefit for patients undergoing EVAR compared to open surgery suggesting that this paradigm shift should not influence overall mortality trends. Other limitations of this study include the use of civil registration system mortality information from which completeness of data varies between countries and that AAA mortality has over time risen and fallen [67,81-83](not behaved linearly) however, the time points included into this study occur within the mortality decline for many of the countries included and the analysis performed takes into account both of these limitations. Mortality from aortic rupture can be missed unless a post mortem is carried out therefore it is possible that AAA mortality is underestimated however this should affect all included countries equally.

Summary

1. **The largest population based analysis of AAA mortality to date**
2. **Mortality from AAA is not declining globally and is not equal between genders**
3. **Trends in mortality are associated with trends in cardiovascular risk factors**
4. **The decline in mortality appears to be more profound in the under 75 age group.**

2.2 Differences between thoracic and abdominal aortic aneurysm

Although mortality from AAA is declining, recent reports have suggested an increase in the prevalence of thoracic aortic aneurysm (TAA) as measured by hospital admissions and operative repairs. Global trends are currently unknown and risk factors driving any change are unclear.

Thoracic aortic aneurysm (TAA) may be defined as a localised or diffuse dilatation of the aorta to at least 1.5 times its normal calibre and may affect the aortic root, ascending aorta, aortic arch or descending aorta. Olsson *et al*[84] analysed the Swedish national healthcare registers (1987 to 2002) revealing that the prevalence of thoracic aortic disease were higher than previously reported and increasing. Similarly Von Allmen and colleagues[85] demonstrated that hospital admissions in the UK (1999 to 2010) for thoracic aortic disease had increased. Despite this, total mortality from thoracic aortic disease in the UK had declined in the same time period and this decline has not been reported elsewhere. Dias *et al*[86] found that mortality from thoracic aortic disease in São Paulo State has steadily increased (1998 to 2007).

Evidence exists that the aorta is a heterogeneous structure with varying influences above and below the diaphragm[87] for example atherosclerosis has been shown to affect the aorta differently with the thoracic aorta appearing more resistant to plaque formation compared to the abdominal aorta. Differences may exist between the epidemiology of TAA and AAA, therefore, aimed to examine global trends in mortality from TAA and to identify associations with trends in established cardiovascular risk factors.

Methods

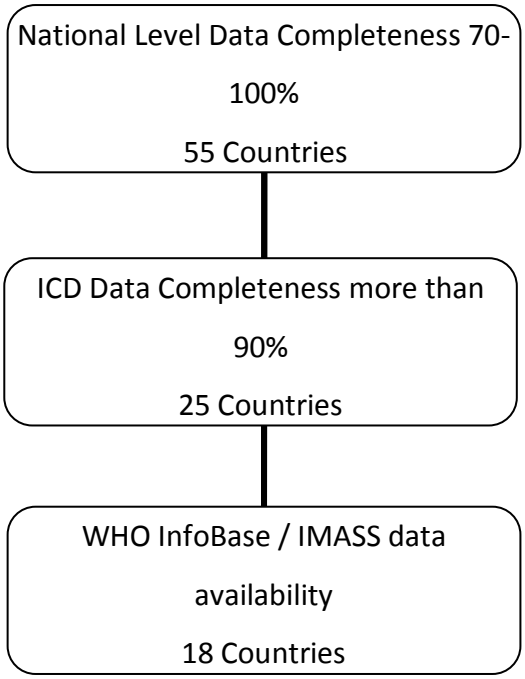
Identification of mortality rates and risk factor trends.

Information relating to the ICD-10 codes I71.1, I71.2, I71.8, and I71.9 which represent thoracic aortic aneurysms of unspecified site (ruptured or otherwise) were extracted from the WHO mortality database on 07/11/2013. Aneurysms of unspecified site were included within this analysis to ensure that all lesions involving TAA were captured in the analyses. No age restrictions were placed and all available data was extracted for analysis. Mortality data for each year varied between countries (range 1994-2010). The methods used for conversion of deaths into age-standardised rates of mortality and risk factor trend has been discussed earlier.

Countries included

After exclusion of countries based on completeness of statistics and availability of risk factor data the following eighteen countries were included in this study: Australia, Austria, Canada, Denmark, Finland, France, Germany, Hungary, Israel, Japan, The Netherlands, New Zealand, Norway, Romania, Spain, Sweden, UK and USA (Figure 2.8)

Figure 2.8 – Flow Diagram of included countries



Statistics

The statistics used within this analysis been discussed in the previous section. Age standardised total (male and female) deaths per year were calculated for each country in both TAA and AD. The peak age at which mortality occurred was calculated over the years 2001 and 2009 and compared. The proportion of age standardised mortality occurring over the age of 75 was compared between years.

Results

Trends in mortality from TAA

This study demonstrates a substantial amount of variability in age standardised mortality from TAA in both males and females (Figure 2.9). Mortality appears to be generally declining in both males and females with the sharpest declines observed in Canada (9.5%),

Netherlands (9.7%) in males, and Australia (7.0%) and the UK (5.5%) in females. Mortality is however not on the decline globally as evidenced by increases in age standardised TAA mortality in Denmark, Hungary, Japan and Romania in males and additionally Austria in females. In Austria a decline was noted in male age standardised mortality with an increase in females.

The most common age range at which mortality from TAA occurred was 75-79 years in 2001 although variation existed for example between Japan (80-84 years) and Romania (60-64 years). In 2009 the most common age range at which mortality from TAA occurred remained at 75-79 years however 13/18 countries demonstrated an increase in the proportion of age standardised deaths occurring above the age of 75 suggestive of a delay in age at death from TAA.

The association of trends in TAA mortality to trends in risk factors

Regression analysis suggests that trends in systolic blood pressure (Figure 2.10a, P = 0.016) and blood cholesterol (Figure 2.11a, P = 0.012) are positively and significantly associated with trends in male age standardised TAA mortality. Trends in body mass index (Figure 2.12a, P = 0.021) demonstrate negative, significant associations with TAA mortality whilst trends in smoking prevalence (Figure 2.13a, P = 0.282) and fasting blood glucose (Figure 2.14a, P=0.394) are not significantly associated with male TAA mortality. Similarly in females, regression analysis of trends in systolic blood pressure (Figure 2.10b, P=0.013) and blood cholesterol (Figure 2.11b, P=0.033) demonstrate positive and significant associations with trends in age standardised TAA mortality. Body mass index demonstrates negative, significant associations with TAA mortality (Figure 2.12b, P=0.024) and no association was

demonstrated with trends in smoking prevalence (Figure 2.13b, P=0.069) or fasting blood glucose (Figure 2.14b, P=0.681).

Figure 2.9 - Trends in male (a) and female (b) age standardised TAA mortality with standard errors.

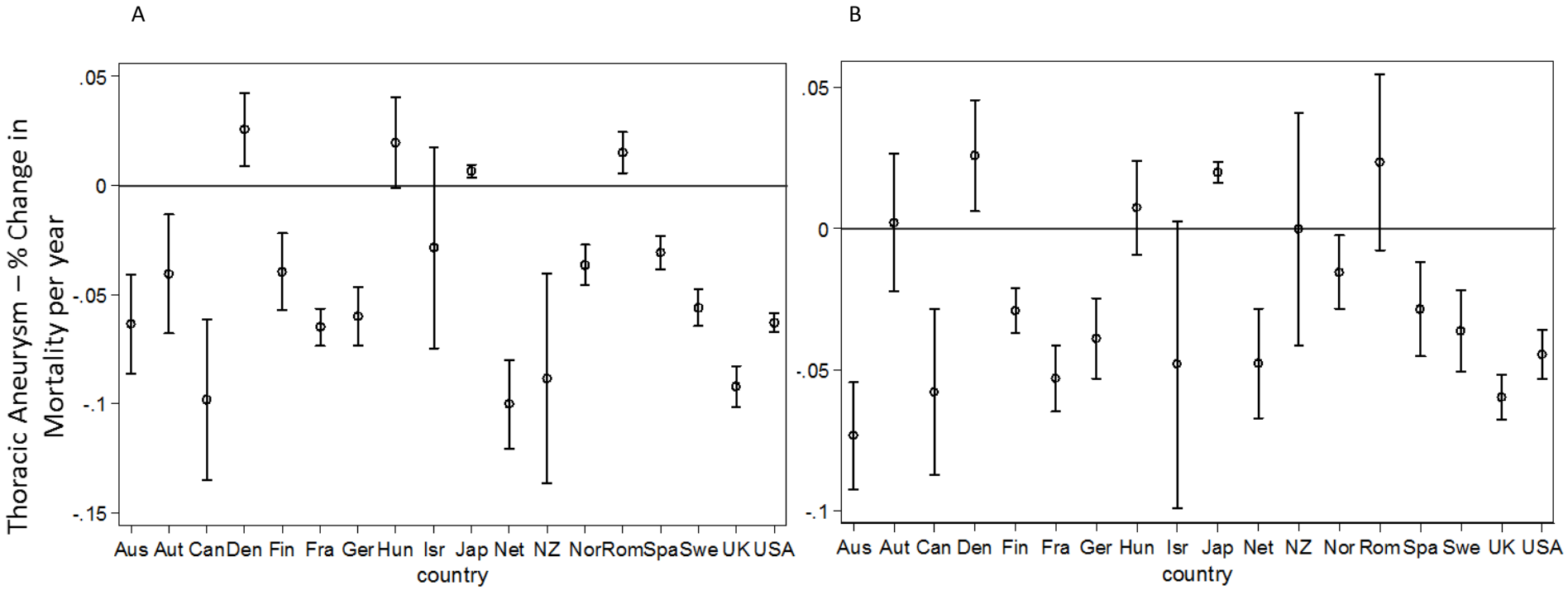


Figure 2.10 – Linear regression revealing the positive association between temporal trends in male (a) and female (b) mean systolic blood pressure and TAA mortality.

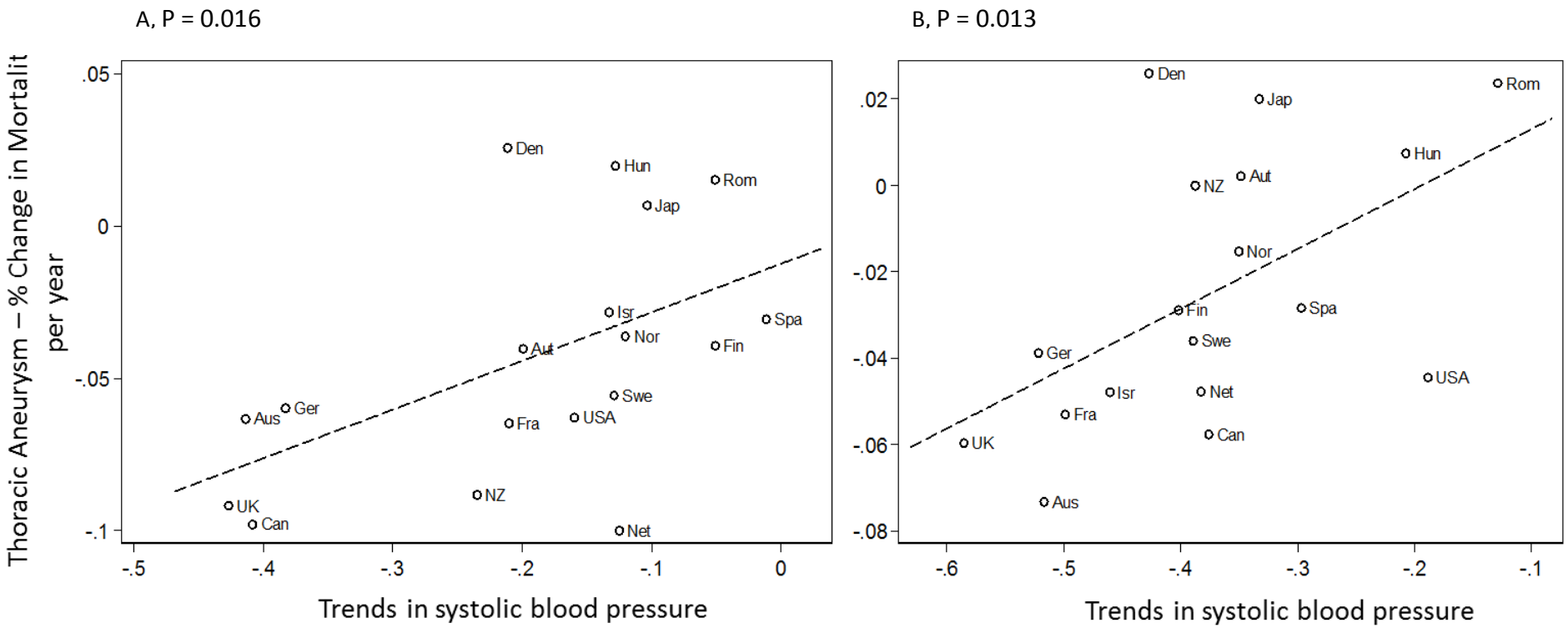


Figure 2.11 - Linear regression revealing the positive association between temporal trends in male (a) and female (b) mean total cholesterol and TAA mortality.

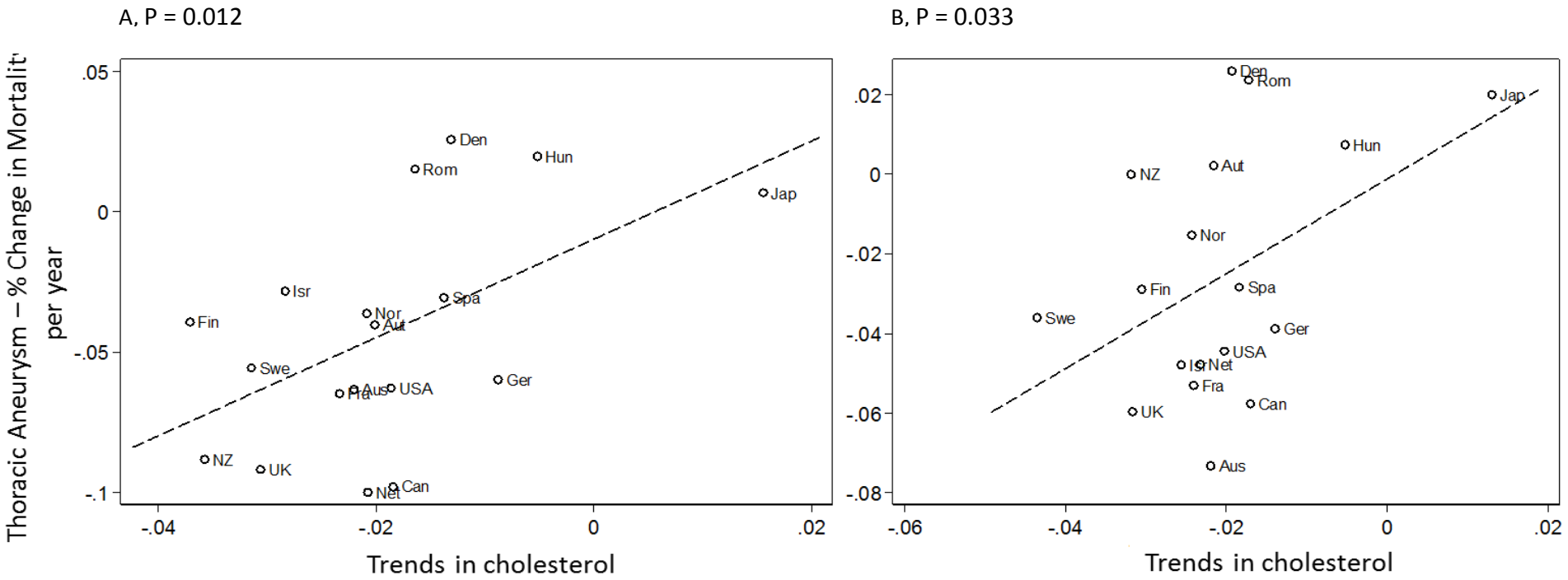


Figure 2.12 - Linear regression revealing the negative association between temporal trends in male (a) and female (b) mean body mass index and TAA mortality

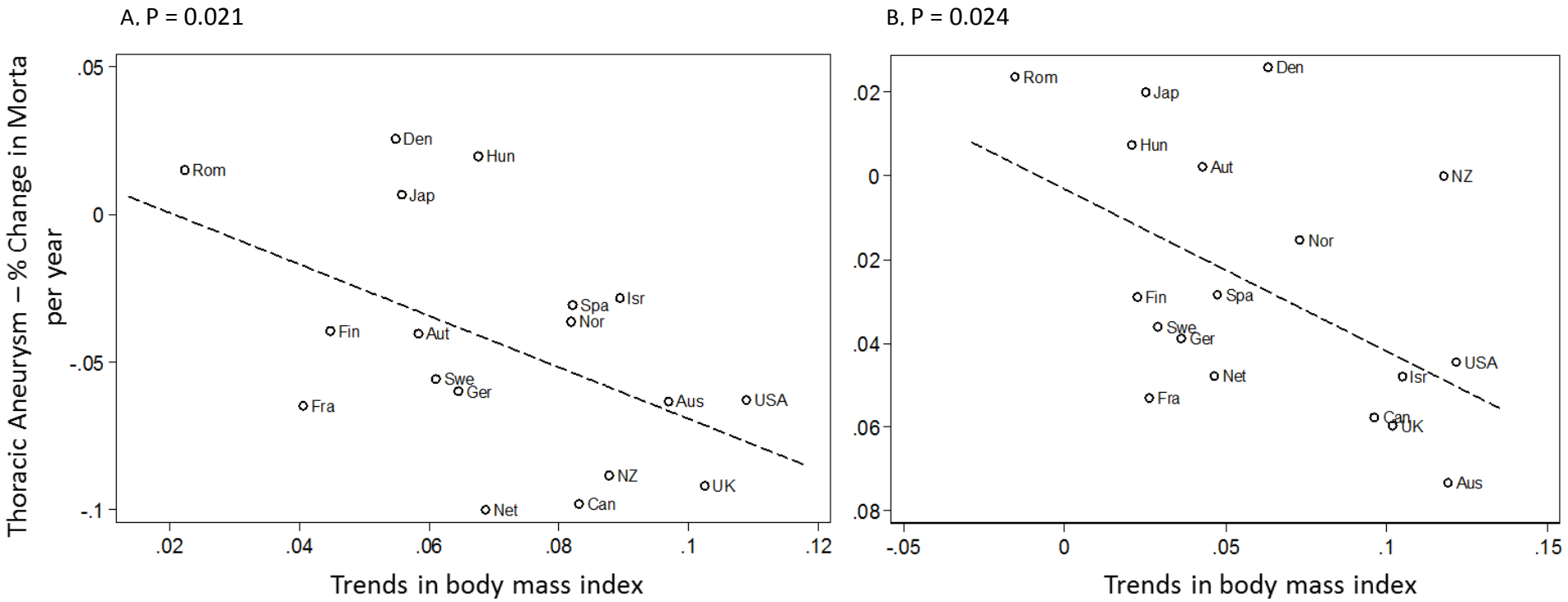


Figure 2.13 - Linear regression revealing the positive association between temporal trends in male (a) and female (b) smoking prevalence and TAA mortality.

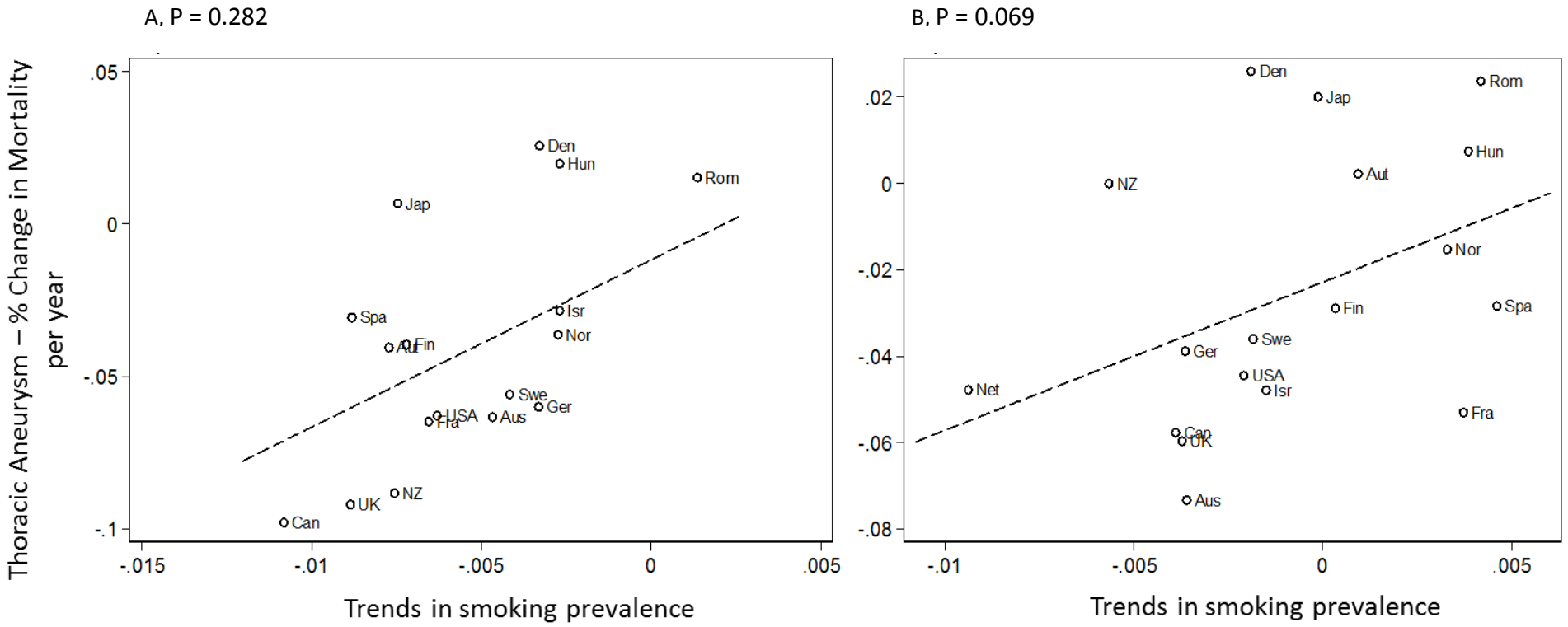
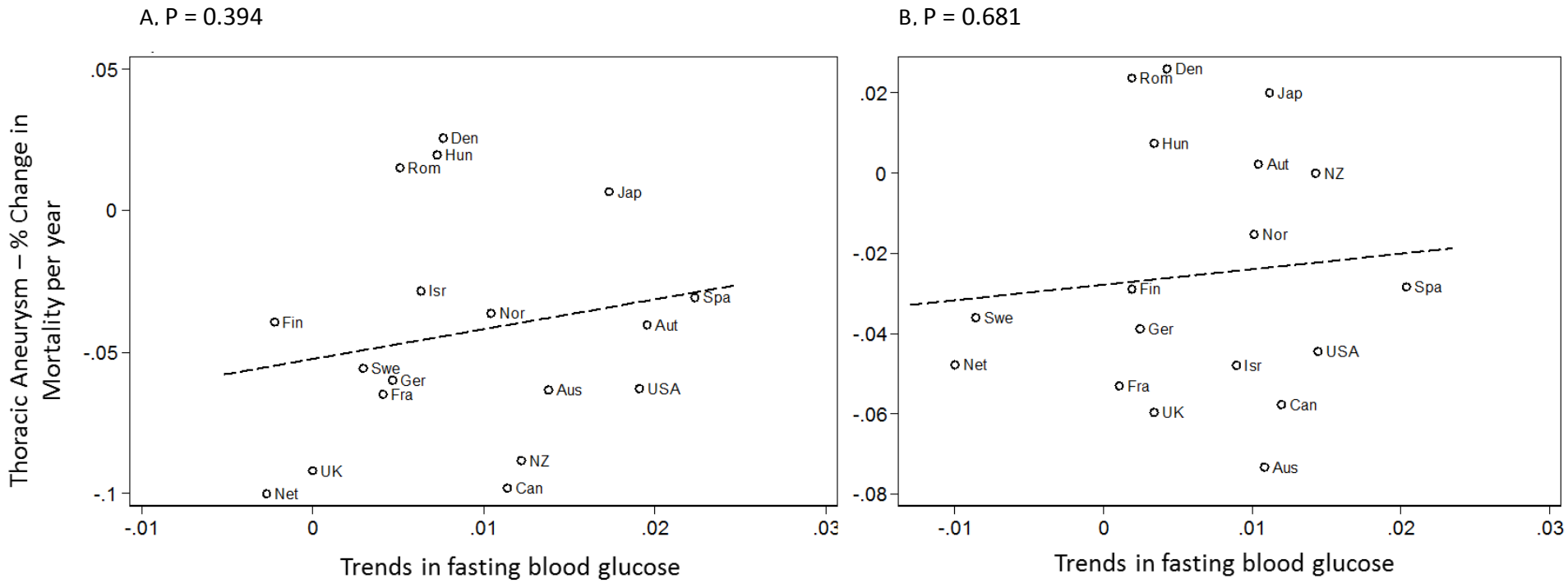


Figure 2.14 – Linear regression revealing no association between temporal trends in male (a) and female (b) fasting blood glucose and TAA mortality.



Discussion

This ecological regression represents the largest population based analysis of mortality from TAA and confirms that mortality secondary to this pathology is generally on the decline. This decline was however, not equal between countries, gender or age groups and some countries demonstrate increases in mortality. Analysis of global variations in common cardiovascular risk factors suggests that the heterogeneity in mortality between countries may be secondary to trends in population blood cholesterol levels, systolic blood pressure and body mass index. The lack of any significant association of TAA with global trends in smoking prevalence may suggest a difference in aetiology compared to AAA.

Male and female mortality from TAA is generally on the decline however large differences are noted. Japan, Romania, Denmark and Hungary demonstrate increasing mortality in both males and females whilst the sharpest declines were seen in Canada and the UK (male and female). Furthermore, within country variations were observed between males and females. These differences may reflect differences in risk factor exposure for example differences in serum cholesterol concentrations across populations and over time. A recent population based systematic analysis of worldwide mean total cholesterol levels[60] highlighted differences in cholesterol levels between genders and demonstrated opposite trends in Australasia, North America, and Europe, where serum total cholesterol decreased from high concentrations, compared to East and Southeast Asia and the Pacific, where it rose from low concentrations. In this study Japan demonstrated increases in TAA mortality.

Another population based analysis [61] of health examination and epidemiological studies revealed males and females in Western Europe had the highest mean systolic blood pressures and that differences existed between genders. It may be expected that

geopolitically close countries for examples Denmark and Sweden would demonstrate similar trends in mortality however this was not the case. The results of this study suggest that these differences may be secondary to risk factor exposure for example the most recent WHO Report on the Global Tobacco Epidemic (2013)[39] suggests that Denmark has a current smoking prevalence of 20% whilst Sweden's smoking prevalence is 11%. Current mean total cholesterol levels[63] are 5.5 and 5.4mmol in men and women respectively in Denmark and 5.2mmol, 5.0mmol respectively in Sweden therefore real differences appear to exist.

The lack of any association between global trends in smoking prevalence and mortality from TAA adds to evidence that the aorta is a heterogeneous structure with varying influences above and below the diaphragm[87]. Smoking is the main modifiable risk factor that has been associated with the development, expansion[30,31] and rupture of AAA[32] however no such association has been proven for TAA. Atherosclerosis has been shown to affect the aorta differently above and below the diaphragm with the thoracic aorta appearing more resistant to plaque formation compared to the abdominal aorta. Some have attributed these observations to differences in flow and shear stress[88] however differences have also been noted in the level of proteases and immune mediators[87] therefore genetic differences may exist. The association of TAA mortality with trends in body mass index is similar to that demonstrated previously for AAA however should be interpreted with caution.

There are a number of limitations to this study for example these results do not exclude the possibility of extrinsic factors influencing population trends in mortality including the use of antihypertensive and lipid lowering medication, however, these effects are taken into account in that they effect population distributions of each relevant risk factor. Statins may reduce TAA growth rate[89] and the proportion of TAA progressing to dissection, rupture, or

death[90] which could affect overall mortality. TAA and aortic dissection are both associated with a number of familial genetic diseases the prevalence of which may vary between countries and changes in the treatment of TAA have occurred over time however current evidence suggests that thoracic endovascular aortic repair has similar long-term results as open thoracic aortic repair[91]. Analysing the impact of an increased use of thoracic endovascular aneurysm repair (TEVAR) for TAAs is not possible in the global setting as such data are not available, however, Von Allmen and colleagues[85] demonstrated that in the UK and there was no association between an increasing use of TEVAR and a decline in mortality. The regression of aggregate, country level data is a well-established method known as ecological regression, the main limitation of which is that it assumes findings from a country also apply to an individual within that country, however, this may not always be the case. This is termed the ecological fallacy. As individual patient level data is not currently available, ecological regression may be useful to make as much sense as possible from the available data

Another limitation of this study is the use of civil registration system mortality information from which completeness of data varies between countries although we did exclude countries with inadequate completeness of statistics and/or in availability of risk factor data. Sensitivity analysis to check the stability of this analysis across age bands are not possible as although mortality data is available by age group, risk factor data is not. There are several heritable disorders that affect the thoracic aorta predisposing patients to TAA, however, ICD-10 does not differentiate between these and those aneurysms secondary to atherosclerosis. The most common of these disorders are Marfans syndrome which has a prevalence of 2-3 per 10,000 individuals[4] and Ehlers Danlos Syndrome which effects approximately 1:25,000

patients[5] therefore both are rare, however, may account for up to 20% of patients with TAA[92]

Summary

1. **The largest population based analysis of thoracic aneurysm mortality**
2. **Mortality from TAA is generally declining much like seen for AAA.**
3. **Clear associations with trends in population cholesterol and blood pressure and body mass index.**
4. **No association with changes in smoking prevalence.**
5. **Public health measures could further reduce mortality from thoracic aortic aneurysm**

Chapter 3: Abdominal Aortic Aneurysm Repair

History

In the previous section I have discussed risk factors for the development of AAA and current epidemiological trends. The reduction noted in the number of patients dying from AAA across many developed countries in addition to evidence that clinically relevant AAA are in the future likely to occur in older patients (due to risk factor modification) may mean that we see fewer patients who are physiologically less fit for surgery. The evolution of AAA surgical repair in many ways demonstrates a number of important paradigms within surgery and highlights the wider evolution from traditional open operative techniques to modern minimally invasive procedures. In this section I discuss the history, current concepts and possible future technologies for the repair of AAA.

Indication for surgery

Despite overwhelming evidence of a benefit to AAA repair compared to non-intervention, the point at which intervention should be offered is less clear. AAA size is the single most important factor in determining the risk of rupture and patients with large aneurysms (more than 5.5cm) are usually offered surgery providing they are fit enough. Lederle and colleagues[93] demonstrated that the 1 year risk of rupture is 9.4% for AAA of 5.5 to 5.9 cm, 10.2% for AAA of 6.0 to 6.9 cm (19.1% for the subgroup of 6.5-6.9 cm), and 32.5% for AAA of 7.0 cm or more. Comparatively, the rupture rate of small AAA (3.0-5.5 cm) appears to about 1% per year or between 0 and 1.61 per 100 person-years[94].

Two large randomised controlled trials, one in the UK[95,96] and one in the USA[97] have compared the strategy of early elective open surgical repair compared with surveillance in patients with small AAA (4.0-5.5cm). These studies demonstrated no survival advantage in

patients undergoing early elective open surgery with similar findings after 12 years of follow up in the UK Small Aneurysm Trial[80]. Furthermore, the Comparison of Surveillance Versus Aortic Endografting for Small Aneurysm Repair trial[98] demonstrated similar findings with no advantage to early endovascular aneurysm repair (EVAR). Patients with asymptomatic AAA that are less than 5.5cm are therefore, usually monitored ultrasonographically rather than offered surgery. Some evidence exists that women are more likely to rupture at a smaller AAA diameter however there is debate about whether this should equate to women being offered surgery sooner.

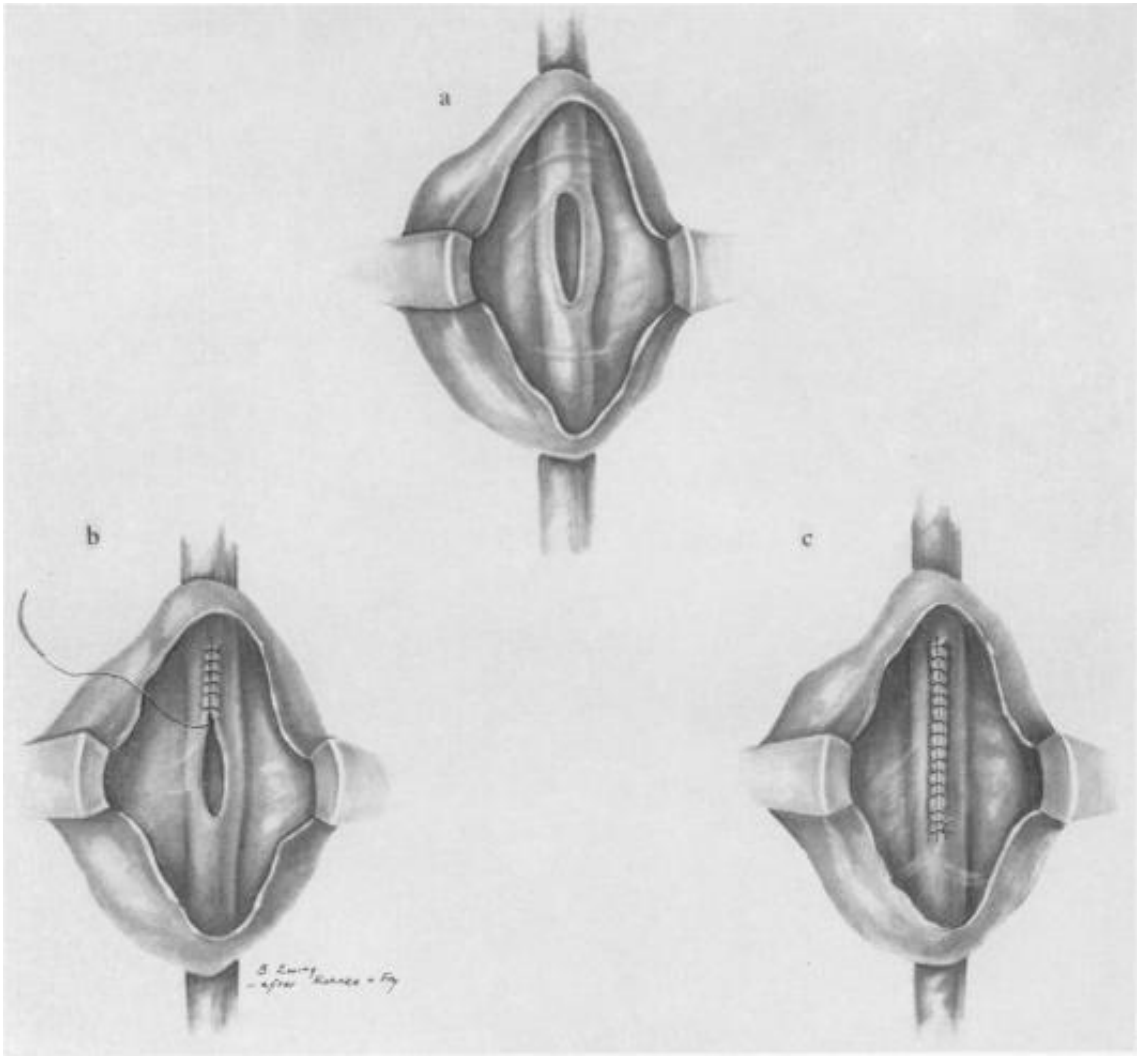
3.1 Open Aneurysm Repair

In the 18th Century William and John Hunter made significant advances in both the physiology and surgical repair of blood vessels laying down the foundations for modern aneurysm repair[99], and it was one of John Hunters students Astley Cooper who became the first surgeon to ligate the abdominal aorta, doing so for a ruptured iliac aneurysm in 1817. In 1888, the concept of endoaneurysmorrhaphy was developed by Rudolph Matas, who spoke before the American Surgical Association in 1902 on "An operation for the radical cure of Aneurysm, based on Arteriorrhaphy"[100]. He discussed securing haemostasis by the application of traction sutures around the artery above and below the aneurysm before making a longitudinal incision to open the sac widely and manually removing any clot or debris.

Matas then described obliterating the aneurysmal sac and oversewing collaterals, whilst preserving a lumen for blood flow[101] (Figure 3.1). Critically this technique reduced damage to branches arising from the aneurysm and adjacent structures while avoiding the potential complications of removing the aneurysm itself. By 1909 Matas had published a case series

of 85 patients having undergone endo-aneurysmorrhaphy with a case fatality rate of 2.3%, significantly lower than the 10% case fatality rate for other available AAA repair techniques[100], thus within 10 years of its introduction the merits of the intrasaccular method for treating aneurysms were established.

Figure 3.1, Technique for restorative aneurysmorrhaphy developed by Rudolph Matas. Note that a lumen is preserved and the aneurysm is plicated. Reproduced with permission from *Ann Surg*, 1966[100]



Despite this, several other novel techniques were attempted in the 20th century to repair AAA including external compression, and polyethene cellophane wrapping[2]. Most notably Albert Einstein was operated on by Rudolf Nissen using cellophane wrapping in 1949, though he eventually died 6 years later when the aneurysm ruptured. Alexis Carrel pioneered anastomotic techniques, receiving a Nobel Prize in 1912 for demonstrating the feasibility of suturing arteries and with these techniques established aneurysm repair could be conducted

by suturing a graft to the aorta proximal and distal to the aneurysm, which was first performed in 1952 by Dubost[2]. The use of aortic allografts as aortic replacement was widely accepted in the early 1950s; however the inevitable aneurysmal degeneration of these grafts led to the development of prosthetic vascular conduits[102].

The first vascular conduit was conceived by Voorhees in 1952, and its textile was a Vinyon "N" polymer (used in parachute cloth). Other materials have been tested such as Nylon and Ivalon however these materials fell into disuse because of their structural instability[102,103]. Polyethylene Terephthalate (Dacron) became clinically available in 1957[102] shortly before Teflon (originally used as electrical wire insulator) and underwent a series of modifications from knitted Dacron to the reliable, durable woven form that is in common use today.

3.2 Endovascular Aneurysm Repair

The most significant recent advance in AAA surgery occurred when Juan Parodi based at the Cleaveland Clinic, USA reported his experience with endoluminal repair of AAA using a stent-graft device in 24 patients in 1991[104], thus beginning the modern era of minimally invasive vascular surgery. Separately Dr Nicholas Volodos had been developing a similar technology in Kharkov, Ukraine where he undertook the first endovascular repair of a thoracic aortic aneurysm. Parodi's introduction of a custom-made Dacron tube endoprosthesis, inserted transfemorally allowed placement of the prosthesis and exclusion of the AAA from the circulation under local or limited epidural anaesthesia and without the morbidity associated with a high regional block, or general anaesthetic[104].

His early straight graft system (Figure 3.2) required 2cm of non-aneurysmal distal aorta to safely seal the stent, however, this site commonly developed problems with distal sealing

due to progression of the aneurysmal process. If the aneurysm was aorto-iliac then a longer prosthesis was required with the contralateral iliac artery excluded via transcatheter balloon or surgical ligation of the external and internal iliac arteries therefore crossover femoro-femoral was grafting was required to complete the procedure[105] (Figure 3.3). In 1995 White introduced the use of single component bifurcated endografts[106] which soon gave way to modular component systems with supported prostheses and smaller, more flexible introducing systems, many of which have evolved to become the devices of choice today.

Figure 3.2, Completed aorto-aortic endograft, Reproduced with permission from *Ann Vasc Surg, 2004*[105]

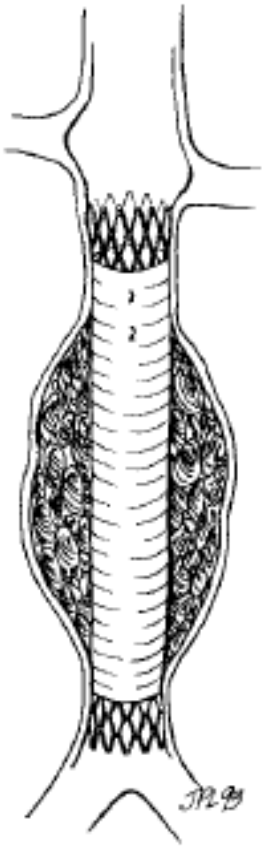
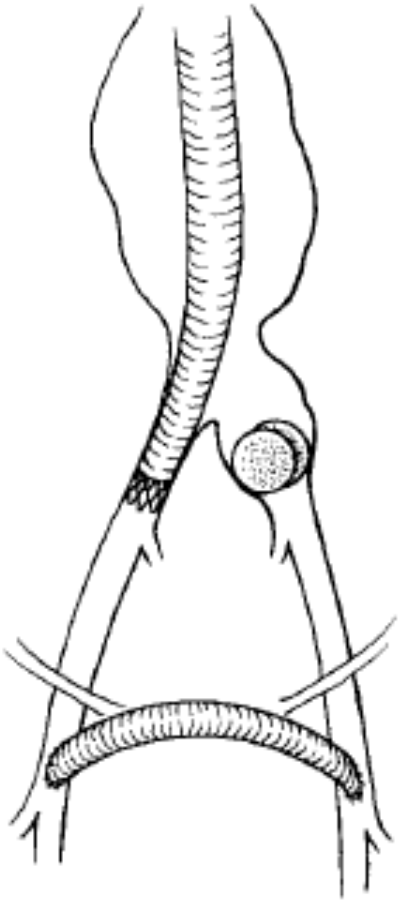


Figure 3.3, Crossover grafting and contralateral iliac exclusion .Reproduced with permission from *Ann Vasc Surg 2004*[105]



Endovascular aneurysm repair (EVAR) has since become established as the treatment of choice for most suitable patients in many vascular centres. Four similar randomised controlled trials (RCT) have been undertaken to determine both the short and long-term outcomes of EVAR compared to open surgical repair (OSR). With ten-year outcomes awaited, these trials have highlighted a significant reduction in 30-day operative mortality[107] and length of stay in favour of EVAR[108]. Audit data from the Outcomes after Elective Repair of Infra-renal Abdominal Aortic Aneurysm report suggests that EVAR has a 3-fold lower perioperative mortality than open repair 0.9% *versus* 4.3%. Despite the promising short term results from the randomised controlled trials, medium and long term follow up from these trials vary, with some showing the early survival benefit of EVAR may be lost over time. A number of concerns have arisen regarding the long-term durability of EVAR, and this in addition to a need for lifelong surveillance, and the added cost of EVAR may negate any early survival advantage gained[109]. A recent meta-analysis[27] analysed the results of the EVAR trials [110-113] and 2 large validated databases [114,115] revealing that there is no long-term survival benefit for patients undergoing EVAR compared to OSR for AAA. It also identified a significantly higher risk of re-intervention and aneurysm rupture post EVAR, challenging the long-term durability of EVAR.

One criticism of the RCT's however was that recruitment into these trials was completed several years ago. Significant improvements have occurred in both operator experience and stent-graft design, allowing EVAR to be achieved in more complex aortic anatomy and in patients previously deemed unsuitable. There have also been improvements in both monitoring and patient optimisation before surgical intervention, thus decreasing length of hospital stay, and improving outcomes for patients undergoing both open and endovascular

intervention. As stent-graft designs have improved, and clinicians have become more adept at inserting endovascular devices, standard stent-grafts have been inserted for shorter, more angulated, and wider aortic necks, outside of manufacturer's instructions for use (IFU)[116]. Generally speaking the anatomical factors which need to be taken into account when planning an EVAR include the diameter and length of the infrarenal aorta, the neck of the aneurysm and the diameter, length and tortuosity of the iliac arteries. Most manufacturers (IFU) state that EVAR should be performed in patients with an aortic neck greater than 15mm length, less than 28mm diameter, and with an angulation less than 60 degrees[117]. This requirement however excludes up to 50% of patients with aortic aneurysms[118] which is one reason for choosing OSR over EVAR.

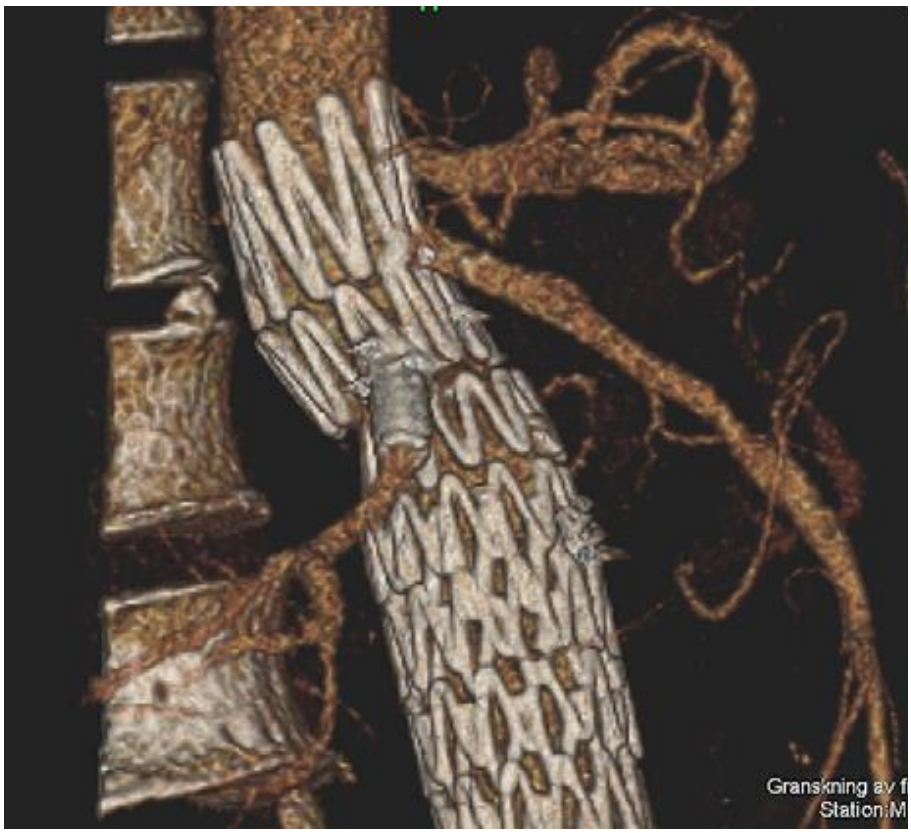
This evolution of EVAR has led to improvements in the care of AAA under both elective and emergency circumstances; however its use in the emergent setting is an area of intense debate. A number of limitations exist to prevent EVAR's common use in emergencies including, the availability of preoperative CT, an off the shelf endograft and a fully staffed operating room equipped to perform emergency EVAR, however some studies have shown that if these problems can be surmounted then there may be a benefit to the patient[119]. Single centre mortality rates for EVAR in ruptured AAA repair show a vast amount of variation with some centres reporting 0% mortality while others reported 54% mortality [120]; however a recent meta-analysis revealed a pooled mortality of 24.3%[121]. The IMPROVE trial[122] randomised 613 patients with suspected ruptured AAA, in 30 vascular centres, to undergo either EVAR (open repair for patients anatomically unsuitable for EVAR) or open repair. Endovascular repair was not associated with a significant reduction in either 30-day

mortality or cost compared to open AAA repair, however, it did demonstrate the feasibility of endovascular repair for ruptured AAA.

Fenestrated EVAR and Chimney endografts

One limitation of EVAR is the requirement for a suitable proximal neck to 'land' in. Several techniques have been proposed to ensure secure circumferential proximal fixation in patients with short necked aneurysms, including fenestrated EVAR (fEVAR) and chimney grafts (ch-EVAR). Fenestrated stent-grafts were first introduced in 1996 with the idea of extending the proximal sealing zone from the infrarenal to the suprarenal aorta. The simplest fenestrated device has just one fenestration for a renal ostia and a scallop in the covered stent to incorporate the superior mesenteric artery origin (Figure 3.4). As the complexity of the aneurysm morphology increases, a greater number of fenestrations can be customized into the graft, which correspondingly increases the technical challenges of deployment[123]. Ch-EVAR is based on the deployment of a covered or bare-metal stent parallel to the aortic endograft, thereby creating a conduit that runs outside the aortic main endograft, to retain or rescue blood flow into overstented aortic branches along the sealing zones[124]. Limitations of chEVAR include the need for brachial access as a totally femoral approach is not possible and may lead to problems with the endograft's proximal seal.

Figure 3.4 – Segmented reconstruction of a fenestrated EVAR. Reproduced with permission from *EJVS, 2009*[123]



A recent review of fEVAR[125] suggested that this technique has a lower peri-operative mortality compared to OSR and therefore represents an attractive option for patients with AAA morphology that is unsuitable for EVAR. Its feasibility has been clearly demonstrated with high uptake of the technique[125] however there are also limitations, including high costs and a delay in manufacture due to the custom made nature of these devices. The concept of central repositories of readymade off the shelf fenestrated devices is however gaining interest and looks like a potentially realistic prospect in the near future raising some hope for the use of this technology in the emergency setting[126]. In a comparison of both ch-EVAR and fEVAR against OSR *Donas et al*[124] found that early mortality, blood loss, length of stay

and acute kidney injury were all reduced by an endovascular approach, demonstrating the safety and feasibility of these techniques in complex AAA where infrarenal neck anatomy is not suitable for standard EVAR.

Preservation of internal iliac arteries

A circumferential seal at the distal endograft is also important therefore the presence of a common iliac artery aneurysm preventing the achievement of this is another major anatomic challenge to conventional EVAR[127]. In current practice, an aortoiliac aneurysm is often treated with embolisation of the ipsilateral or sometimes bilateral internal iliac artery (IIA). However, this has several reported risks which appear to be more common in bilateral embolisations[128] including, buttock claudication (reported in up to 30% of patients[128]), sexual impotence (reported in up to 17% of patients), and colonic ischemia[129]. In addition IIA occlusion makes the endograft limb patency entirely dependent on femoral outflow, which can be compromised in patients with peripheral arterial disease. Branched iliac devices have been introduced as a way to deal with aorto-iliac aneurysms, allowing effective preservation of antegrade flow from the internal iliac artery, and in the last decade a number of studies[130] have confirmed the feasibility and safety of this novel technique however they are technically difficult and true long term outcome data are awaited.

Endovascular aneurysm sealing

A drawback of many of the devices in current use is that the aneurysm sac itself is left untreated leaving a large potential space and providing an opportunity for the development of endoleaks (I will discuss endoleak in detail in the next section), sac expansion and endograft migration[131]. The Nellix endoprosthesis is an endoluminal device, designed to treat aorto-iliac aneurysms by obliterating the aneurysm sac, thus eliminating this potential

space, while maintaining normal flow to the lower extremities. The endograft limbs are supported within the aneurysm sac by polymer-filled endobags, filling the aneurysm sac, blocking retrograde flow from side branches without the need for proximal and distal fixation[132]. They eliminate the space for potential complications, while anchoring the device within the aneurysm sac to provide positional stability. Initial results from the use of this graft suggests patients with both favourable and adverse aneurysm anatomy could be successfully treated, expanding the population of patients who are candidates for endovascular repair and reducing the number of complications associated with it. However, medium and long term follow up of outcomes from this technique are awaited[133].

Summary

1. **EVAR was first developed in 1991**
2. **Concerns exist over EVAR's long term durability**
3. **EVAR has a higher risk of re-intervention**

Chapter 4: Endoleak after EVAR

Since the introduction in 1991[104] of EVAR, throughout its evolution from a straight graft system to modular component systems with supported prostheses, endoleak has been its Achilles heel. Endoleak may be defined as persistent blood flow within the aneurysm sac following EVAR and are classified according to the source of the blood flow into the aneurysm sac. Some types of endoleak have clearly been associated with an increased risk of further complications and therefore necessitate intervention whilst other types of endoleak are thought to be benign. Within this chapter I will discuss the different types of endoleak followed by an in depth focus on type II endoleak the management of which is hotly debated between vascular centres, internationally. I will present a review of endoleak, their sequela and current management strategies.

4.1 Imaging of endoleaks

Duplex ultrasound scanning (DUSS) and computed tomography angiography (CTA) are the most common imaging modalities utilised for endoleak detection, however, lifelong CT surveillance comes with the cumulative risk of radiation exposure, and an increased risk of contrast nephropathy. Many centres utilise a DUSS first approach [134,135] with CT used to confirm or clarify any complication identified, however, DUSS alone may have a poor diagnostic accuracy in relation to specific types of endoleaks[136]. One approach to improving this is to perform contrast enhanced ultrasound (CEUS) which has been demonstrated to be equivalent with CT at identifying endoleak, although may not be as sensitive in the detection of endograft migration or kinking[137].

Another option includes magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) techniques. These technologies demonstrate excellent soft tissue

contrast, may be more sensitive than CTA[138], and do not rely on ionizing radiation, however are considered time consuming and costly. A recent review[139] of all three modalities found that CEUS was significantly more sensitive and specific than DUSS in the identification of endoleak, more accurate than CTA and of similar accuracy to MRA. Newer techniques using gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA) as a contrast agent for dynamic contrast-enhanced MRI have been shown to further improve the sensitivity of MR in detecting small endoleaks, however whether MR techniques will play more of a role in endoleak detection in the future remains to be seen[140].

4.2 Classifications of Endoleak

Type I Endoleak

Type I endoleak can be defined as a failure to create an adequate circumferential seal at the proximal attachment site (Type Ia endoleak) or the distal attachment site (Type Ib endoleak) allowing a direct communication to exist between the aorta or iliac arteries and the aneurysm sac. The high pressures associated with a type I endoleak result in an ongoing risk of aneurysm growth and rupture therefore re-intervention is often necessary[141]. Poor endograft sizing (diameter and/or sealing zone length)[142] and postoperative complications of EVAR including stent graft migration and expansion of the aneurysm neck, may increase the risk of developing a type I endoleak[143] which have been demonstrated to occur more commonly in patients with complex arterial anatomy including; a short aortic neck (length <15mm), wide aortic neck (diameter >32mm), increased angulation (>60^{o}) and the presence of calcification or excessive thrombus [144] at the endograft landing zones[145]. Some authors[146] suggest that type I endoleak may spontaneously resolve given time[147] and that selected patients may benefit from a conservative approach, however, it is generally accepted that

intervention is required with choice of intervention depends principally on the source of the leak.

Patients with no evidence of endograft migration and a proximal type I endoleak may be treated with dilation of the graft. This procedure aims to open a balloon in the non-expanded part of the endograft where the leak stems from, to enhance endograft apposition with the aortic wall[139]. If the endograft was malpositioned or has migrated then another option would be to place a balloon-expandable stent or cuff, positioned over the proximal portion of the aorta. The aim of this procedure would be to add extra radial strength and coverage to the endograft attachment site. Rajani and colleagues[148] demonstrated a 100% clinical success rate (no further endoleak on follow up) in 24 patients treated with a balloon expandable stent whilst two further retrospective studies have reported a 94%[149] and 100%[150] clinical success rate in fifty four patients combined, over a mean follow-up of eight months and fifty three months respectively. Taken together these studies suggest that balloon expandable stents are an effective intervention for the treatment of proximal type I endoleaks. One limitation to the use of extension stents or cuffs is the anatomy of the aneurysm neck for example the presence of important arterial branches that an extension would occlude. Fenestrated cuffs which like the fenestrated grafts described earlier are designed to ensure blood flow to these arteries, have been used as a viable alternative[151].

Some type I endoleaks may be embolised, aiming to disrupt communication between the inflow and outflow supplying the leak, however, reported clinical success varies. Eberhardt and colleagues suggest that transcatheter embolisation of type I endoleaks using Onyx (Ethylene-vinyl Alcohol Copolymer) is safe with a high success rate in cases where extension

is not possible with similar findings by Chun et al[152,153]. One serious complication of the use of liquid embolic agents is the risk of distal ischemia to non-target vessels, including rare cases of spinal cord ischaemia[154]. One study[155] reported a 100% clinical success rate with the use of microcoils in ten patients (two patients required multiple treatments), however, Maldonado and colleagues[156] reported a lower clinical success rate (75%) with coil embolisation (mean follow up of six months). Another study reported a 92.3% clinical success rate[156] (thirteen patients) over ten months of follow up[153,157] therefore large studies with adequate follow up times are lacking. Type Ib endoleaks can be treated similarly to that described above however, an extension endograft into the distal common or external iliac artery is recommended in cases of a short landing site or iliac artery aneurysm. In cases where endovascular interventions fail, conversion to open surgical repair may be necessary with its associated morbidity and mortality.

Type II Endoleak

This will be discussed in detail within the next chapter.

Type III Endoleak

Type III endoleaks occur secondary to endograft component disconnection (Type IIIa) or stent fabric holes (Type IIIb) and are reported to occur in about 4% of patients at one year[158]. The risk of developing a type III endoleak increases with excessive angulation of the aortic neck or iliac segments therefore one theory is that type III endoleaks may develop following post EVAR morphological changes within the aneurysm sac, placing extra strain on the endograft components and causing subsequent displacement. Type III endoleak may also occur if insufficient overlap exists between the stent graft components[159]. This complication allows arterial flow into the aneurysm sac, therefore type III endoleaks are associated with

continued aneurysm expansion and a high risk of aneurysm rupture[160]. To prevent these outcomes, intervention is recommended[161].

Type III endoleaks are often treated endovascularly. One treatment option involves placement of an extension or cuff at the level of the leak[162] for example Van Lammeren and colleagues[163] reported a 67% clinical success rate in nine patients with bridging stents over a type III endoleak (mean follow up of seventy six months). Two patients developed a persistent endoleak and another developed graft obstruction. Abouliatim and colleagues described an intraoperative type III endoleak caused by a tear in the polyester graft successfully treated by relining the original graft with an aorto-uni-iliac device[164]. Similarly, Faries *et al*[165] described placing two ilioiliac and one aortouniliac grafts in three patients with type III endoleak over twenty four months of follow up. This suggests that relining may be more successful than stents for type III endoleak.

Type IV Endoleak

Type IV endoleaks relate to the graft fabric porosity. The leak occurs through the intact, thin walled graft fabric with the vast majority sealing spontaneously within one month, therefore they are thought to be benign in nature. Type IV endoleaks have been demonstrated to not increase the risk of aneurysm rupture; hence treatment is not recommended[166]. However, other types of endoleak must be excluded before diagnosing a type IV leak[162].

Type V Endoleak

A type V endoleak, otherwise known as endotension, has a prevalence of about 5.4%[54] and is defined as a continued high intra sac pressure and sac expansion following EVAR, without evidence of continued aneurysm sac perfusion[167]. The pathogenesis of endotension is uncertain and debate over the aetiology continues with some suggesting that endotension

may occur secondary to an undiagnosed endoleak[168]. Several mechanisms for pressure transfer to the aneurysm sac have been described[169] including graft material porosity allowing for ultrafiltration of blood across the stent graft and the transmission of pressure across thrombus to the aneurysm wall. In the short term endotension has not been associated with a high risk of aneurysm rupture[159]; however, continued aneurysm sac enlargement increases this risk[170]. Where intervention is thought to be necessary[171], options include the use of extension cuffs, relining the original stent graft with another graft or open surgical conversion. Extension cuffs have been described in three case reports demonstrating 100% clinical success over a 6 month follow up period[172]. One study described relining the endograft with another endoprosthesis and reported a 100% clinical success rate in five patients over a mean follow up of sixteen months[173]. Conversion to open repair may be necessary when no clear cause for the endotension can be identified, and endoleak cannot be ruled out as a cause of sac expansion.

Summary

1. **Duplex ultrasound is a common first line imaging modality for diagnosing endoleaks**
2. **Type I and III endoleak are associated with sac expansion and rupture**
3. **Type IV and V endoleaks have not been demonstrated to increase the risk of rupture**

4.3 Type II endoleak – A review

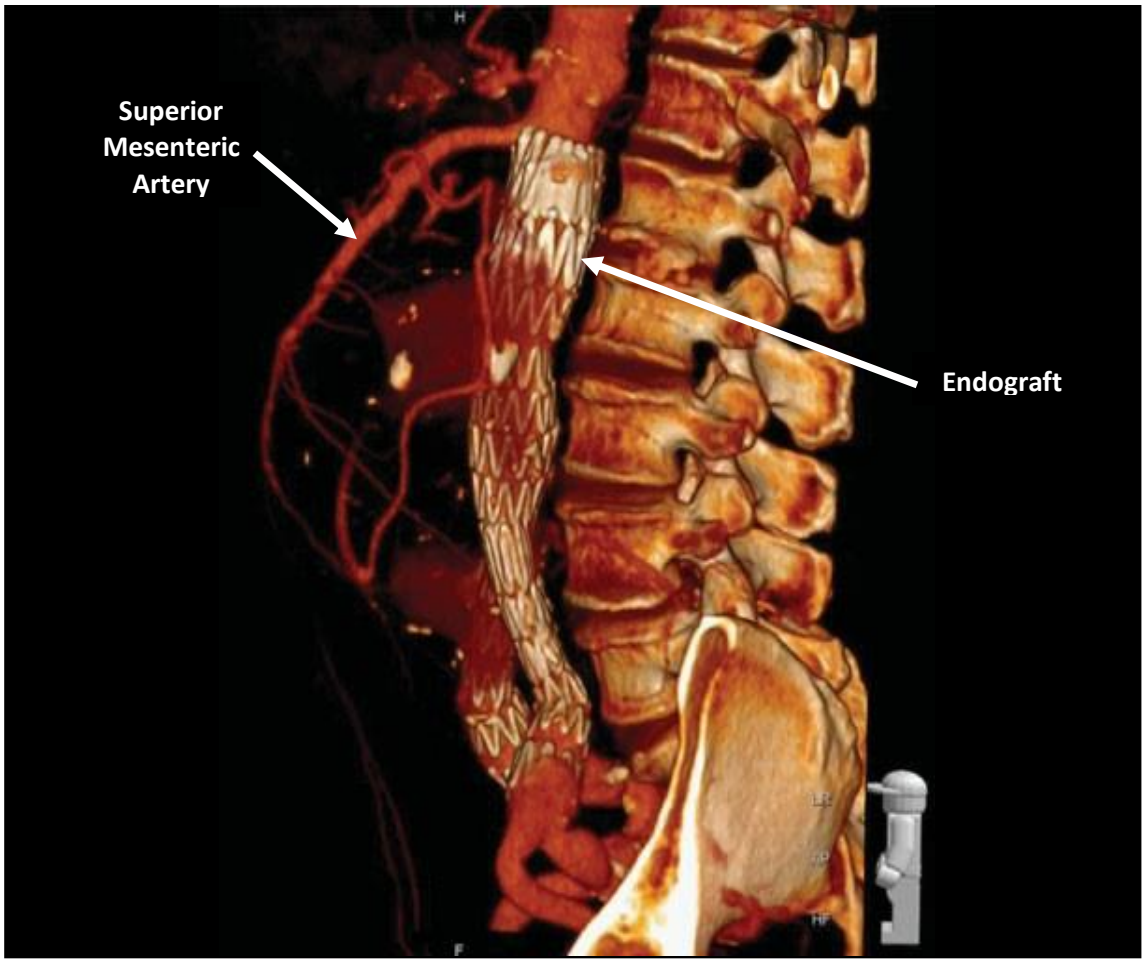
Type II endoleak is the most common complication post endovascular aneurysm repair (EVAR) accounting for up to 44%[174] of all endoleaks, however the natural history and significance of type II endoleaks remain uncertain with some experts considering them to be a benign complication[175] whilst others have associated type II endoleak with continued aneurysm sac expansion and rupture[176,177]. A gold standard treatment strategy for patients with this complication is lacking, therefore, within this chapter I review the current literature on this common but complex complication of EVAR.

Type II endoleak may be defined as the backflow of blood from aortic collateral arteries into the aneurysm sac, most commonly involving the inferior mesenteric and lumbar arteries (Figure 4.1). Risk factors for the development of a type II endoleak include an increased number of patent aortic collateral arteries, large aneurysm diameter and increasing age whilst current smoking and decreased ankle-brachial index are associated with a lower risk[178,179]. Those patients with malignancies, coronary artery disease or chronic obstructive pulmonary disease demonstrate higher rates of spontaneous endoleak sealing with about a third of all isolated type II endoleaks spontaneously resolving over time[180]. A lack of controlled trials addressing intervention post EVAR has led to treatment algorithms being based solely on anecdotal experience[175] or retrospective studies leading some centres to advocate a conservative approach while others support the aggressive treatment of all type II endoleaks to prevent aneurysm expansion and rupture.

Several treatments are available for type II endoleaks including conversion to an open surgical repair, embolisation and laparoscopic clipping, however, the two most common approaches are transarterial embolisation and translumbar embolisation. The aim of this

systematic review was to analyse the risk of rupture and outcomes of interventions in patients with isolated type II endoleaks.

Figure 4.1 Lateral computed tomography reconstruction of the abdomen and pelvis showing an endovascular aneurysm repair with two type II endoleaks visible as red blushes of contrast anterior to the aortic stent graft. No aneurysm sac is visible due to the type of windows used.



Methods

Standard PRISMA guidelines[181] were followed and documented in advance in a formal protocol.

Eligibility Criteria

All studies reporting on type II endoleaks were considered for full text review and any potentially duplicate data was taken into account within the analysis.

Information Sources

Medline, Embase, and Health and Psychosocial science databases were searched on 13/8/2012 from 1946-2012 using OVID online. The terms 'type II endoleak' OR 'type 2 endoleak', 'embolization' OR 'embolisation', 'endovascular' AND 'aneurysm' AND 'management' AND 'rupture' were searched. The reference lists of selected articles were also manually searched to identify relevant articles.

Study Selection

Two reviewers (myself and a clinical fellow) working independently determined trial eligibility and extracted descriptive, methodologic, and outcome data from each eligible study, using a standardised form. From each study the reviewers extracted the following (a) publication year (b) country of origin (c) number of patients (d) study design (e) mean follow up (f) incidence of type II endoleak (g) number of interventions performed (h) clinical success of the interventions (i) sac change (j) number of repeat interventions (k) number of complications (l) number of conversions (m) number of ruptures.

Potential Bias in Primary Studies

The Newcastle Ottawa scale was used to ensure the quality of non-randomised studies and this review only included papers that scored ≥ 7.

Results

Electronic searches identified 378 articles potentially suitable for inclusion in the review and 32 of these studies were eligible for inclusion (Figure 4.2, Table 4.1). Twenty six studies were retrospective reviews from single centres, 5 were retrospective reviews from multiple centres and one was a prospective review from multiple centres. These studies were published over the date range 1994 to 2011. The total number of patients was 21,728 (range 3 to 4291), 392 interventions were performed with a mean follow up ranging from 83 days to 4.8 years. Due to the methodological heterogeneity of the studies included in the review a formal meta-analysis was not performed. 1515 type II endoleaks were reported to have occurred over a range of 10 to 48 months follow up in 14872 patients (10%). All studies used CT imaging to identify type II endoleaks except one [182] which used ultrasound scanning. Spontaneous resolution of a type II endoleak was reported in 244 out of 694 patients (32.3%) over a range of 3 months to 4 years.

Figure 4.2 PRISMA diagram for the systematic review

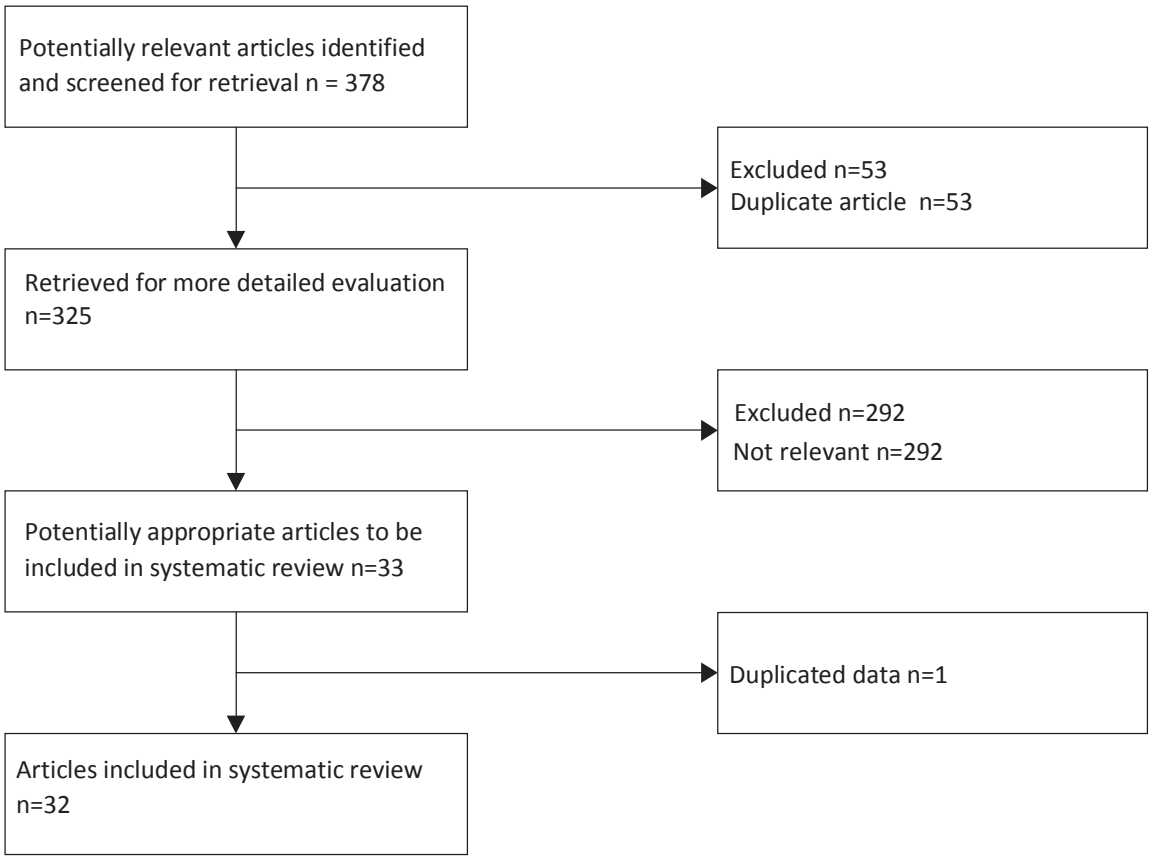


Table 4.1 Characteristics of included studies

Reference	Year	Criteria for treatment of type II endoleak	Follow-up (months)*	Method of detection	No. of patients
Sarac *et al*[183].	2012	Persistence or aneurysm expansion ≥ 5mm	NS	CT	809
Wyss *et al*[176]	2010	NS	57.6	NS	848
Rayt *et al*[182].	2009	Conservative management	48	US	369
Jones *et al.*[177]	2007	Aggressive identification and treatment	38	CT	873
Silverberg *et al*[184].	2006	Sac expansion ≥ 5 mm	22	CT	965
Sheehan *et al.*[185]	2006	NS	36	NS	1909
Tolia *et al.*[186]	2005	Increase in sac diameter ≥ 5mm	30	CT	83
Van Marrewijk *et al*[161].	2004	NS	15	CT	3595
Steinmetz et al[187]	2004	Persistence > 6 months or 5 mm expansion	21.7(±16)	CT	486
Fransen *et al*[188].	2003	NS	12†	NS	4291
Parent *et al*[189].	2002	Sac expansion ≥ 5 mm	20.7(±16.8)	US/CT	83
Buth *et al.*[190]	2002	NS	NS	NS	3529
Tuerff *et al.*[191]	2002	Increase in aneurysm size, persistence > 6 months	15.7	CT	130
Liewald *et al.*[192]	2001	Persistent type II endoleak > 3 months	NS	CT	160
Haulon *et al.*[193]	2001	NS	13.3	CT/MRI	60
Chuter *et al.*[194]		Sac expansion	NS	CT	114
Solis *et al.*[195]	2002	Aggressive treatment	18.2	CT	191
Sampram *et al.*[196]	2003	Increase in sac diameter	12.2(±11.7)	CT	703
Faires *et al*[165]	2003	NS	24.5(±12.2)	CT	597
Farner *et al.*[197]	2003	NS	12 (±2.4)	CT	63
Kasirajan *et al.*[198]	2003	Aggressive treatment	9(±3.2)	CT	104
Zarins *et al.*[199]	2004	NS	36(±11)	CT	398
Carpenter *et al.*[200]	2004	NS	11	NS	227

Stavropoulos *et al.*[201]	2005	Persistent leak > 6 months	3	CT	9
Martin *et al.*[202]	2001	Symptomatic or aneurysm growth	7	CT	64
Rial *et al.*[203]	2004	Persistent leak > 6 months	NS	CT	3
Baum *et al.*[204]	2002	Aggressive treatment of all type II endoleaks	NS	CT	33
Massis *et al.* [205]	2012	Sac expansion ≥ 5 mm within 6 months, sac > 6 cm	**4	NS	95
Sheehan *et al.*[206]	2004	Persistent leak ≥ 6 months	18	CT	28
Aziz *et al*[207]	2012	Persistent type II endoleak +/– sac expansion.	Mean 23	CT	42
Conrad *et al.*[208]	2009	Persistent type II endoleak with sac expansion	35	CT	832
Funaki *et al.*[209]	2012	Persistent type II endoleak with sac expansion ≥ 5 mm	27.5	CT	25

Values are mean(s.d.), except †median. NS, not stated; CT, computed tomography; US, ultrasonography; MRI, magnetic resonance imaging

Sac expansion, conversion and rupture

In this review 21 conversions to open surgical repair were reported for the treatment of isolated type II endoleaks (1.4%, 21/1515) over a range of 11 to 60 months after EVAR. Fourteen of these conversions were reported by 2 papers [190,199] from which 8 were performed for elective repair of unresolved type II endoleaks with sac enlargement.

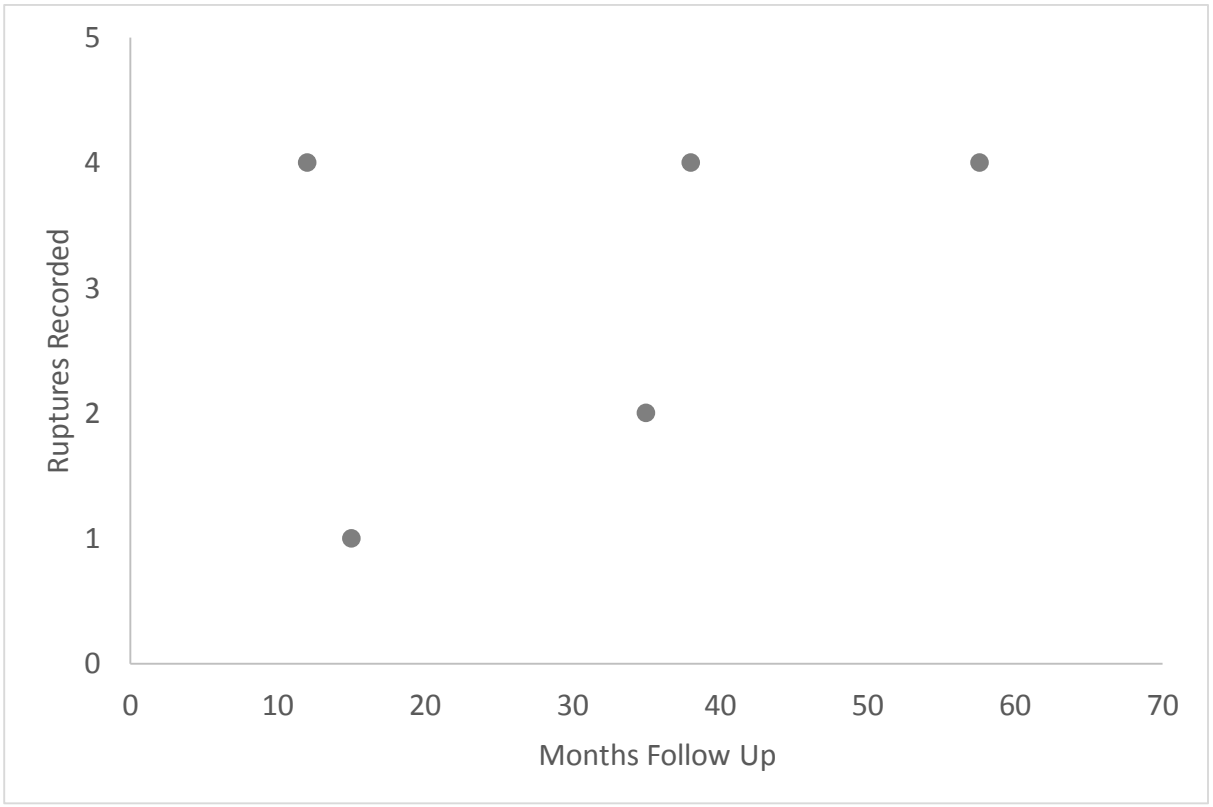
The total number of patients who ruptured post EVAR (Table 4.2) with a known isolated type II endoleak was 14 (0.9% of all type II endoleaks reviewed). Eight ruptures were associated with a type II endoleak and concurrent sac expansion (57%). One rupture was associated with an aneurysm sac that had decreased in size and 2 ruptures were reported in patients with a stable sac. Three ruptures had not commented on any change in sac size. In figure 4.3 I have plotted the number of ruptures in each respective paper against follow up time demonstrating no clear association with follow up time.

Table 4.2, Incidence of type II endoleak and spontaneous closure

Reference	No. of patients	Type II endoleaks	Spontaneous resolution	Conversions	Ruptures
Wyss *et al*.	848	n.s.	n.s.	1	4†
Rayt *et al*	369	25	12	0	0
Jones *et al*	873	164	24	3	4
Silverberg *et al*	965	154	55	0	0
Sheehan *et al*	1909	221	117	0	0
Tolia *et al*	83	15	10	n.s.	0
van Marrewijk *et al**	3595	320	n.s.	n.s.	1
Steinmetz *et al*	486	90	n.s.	0	0
Fransen *et al**	4291	n.s.	n.s.	n.s.	4
Parent *et al*	83	36	13	0	0
Buth *et al**	3529	240	n.s.	6	1
Tuerff *et al*	130	22	7	0	0
Liewald *et al*	160	13	1	1	0
Haulon *et al*	60	18	n.s.	0	0
Chuter *et al*	114	9	n.s.	n.s.	0
Solis *et al*	119	14	1	0	0
Faries *et al*	597	16	n.s.	0	0
Farner *et al*	63	9	0	n.s.	n.s.
Kasirajan *et al*	104	8	n.s.	n.s.	0
Zarins *et al*	424	70	n.s.	8	0
Carpenter *et al*	227	21	6	1	0
Conrad *et al*	832	50	n.s.	1	2

*Three papers were published from the EUROSTAR registry and may present duplicated data. In the assessment of ruptures, only those reported by Fransen *et al*.[21] were included. †One rupture with an associated type II endoleak was excluded as there had been a previous type I endoleak. n.s., Not stated.

Figure 4.3 – Scatter plot demonstrating no association between follow up time and the number of ruptures recorded.



***One rupture (*Buth et al*) could not be included due to no follow up time being published.**

Interventions for type II endoleaks - Translumbar approach

Six studies reported outcomes for the translumbar approach (Table 4.3) with patient numbers ranging from 3 to 95 patients. Different methods were used between studies and mean length of follow up ranged from 3 to 21.7 months between studies.

In total 56 translumbar interventions were performed and clinical success (defined as no recurrent type II endoleak during follow up) was reported in 81% (46/56). Clinical success ranged from 100% in two studies[187,203] (7 patients combined), to 67%[8201] (9 patients in study) which included one patient that required an open surgical repair for continued sac expansion. 53% (30/56) of patients were reported as having a decreasing or stable sac post intervention with 2 patients requiring a further re-intervention. The two studies with the largest number of persistent endoleaks [201,205](9 combined) post translumbar embolisations reported the reasons behind this as unclear.

Table 4.3 Outcomes of translumbar embolisations to treat type II endoleaks after endovascular repair. n.s, not stated.

Reference	Interventions	Clinical success	Persistent or recurrent leak	Secondary intervention	Sac decreased/ stable	Complication	Conversion	Rupture
Stavropoulos *et al* (%)	9	6(66.7)	3(33.3)	2 (22.2)	8(88.9)	0	1(11.1)	0
Martin *et al* (%)	4	3(75.0)	1(25.0)	n.s.	4(100)	0	0	0
Rial *et al* (%)	3	3(100)	0	0	n.s.	0	0	0
Steinmetz *et al* (%)	4	4(100)	0	0	0	0	0	0
Baum *et al* (%)	13	12(92.3)	1(7.7)	0	n.s.	0	0	0
Massis *et al*(%)	24	18(75.0)	6(25.0)	n.s.	18(75)	0	0	0

Interventions for type II endoleaks - Transarterial approach

Seven studies reported outcomes for transarterial interventions (Table 4.4) with patient numbers ranging from 8 to 95 patients. Again methods varied between the studies however the most common indication for treatment was a persistent type II endoleak lasting more than 6 months. Mean length of follow up ranged from 4 to 24.5 months between studies.

In total 120 interventions were performed of which 75 (62.5%) were clinically successful defined as no recurrent type II endoleak during follow up. Clinical success ranged from 15% (3/20) [204] to 89% (16/18)[193]. In total 64% (77/120) of patients were reported as having a stable or decreasing sac post intervention. One conversion to open surgical repair was reported for continued sac expansion and interestingly a larger number of complications were reported post transarterial intervention compared to translumbar including myocardial infarctions and renal impairment.

One study[195] noted multiple mechanisms resulting in clinical failure including the development of new type II endoleaks, persistent blood flow through the coils of the treated endoleak and the development of anastomoses around the previously coiled vessel. Another study[198] noted clinical failure was more likely with patients in whom they were unable to embolise within both the vessel and the aneurysm sac itself.

Table 4.4, Outcomes of transarterial embolisations to treat type II endoleaks after endovascular repair *Includes data from type I endoleaks.

Reference	Interventions	Clinical success	Persistent / recurrent leak	Secondary Reintervention	Sac decreased or stable	Complications	Conversion	Rupture
Sheehan *et al* (%)	19	15(78.9)	3(15.8)	2(10.5)	7 of 28*	0	1(5.3)	0
Kasirajan *et al* (%)	8	6(75.0)	2(25.0)	0	6(75)	1(12.5)	0	0
Haulon *et al* (%)	18	16(88.9)	2(11.1)	0	18(100)	3(16.7)	0	0
Solis *et al* (%)	10	4(40.0)	6(60.0)	2(20.0%)	0	0	0	0
Faries *et al* (%)	16	14(87.5)	2(12.5)	2(12.5)	5(31.3)	8(50)	0	0
Baum *et al* (%)	20	3(15.0)	16(80.0)	9(45.0)	0	0	0	0
Massis *et al* (%)	29	17(58.6)	12(41.4)	12(41.4)	21(72.4)	0	0	0

Overall outcomes for interventions

Analysing outcomes only from the 13 studies which reported outcomes from transarterial and translumbar interventions separately, there were a total of 176 interventions from which 69% (121/176) were clinically successful. A higher proportion of the translumbar group were reported to have a clinically successful procedure (TL 81% v TA 62.5% P = 0.024) with fewer patients having a persistent endoleak post intervention (TA 36% v TL 19% P = 0.04). A further intervention for failed embolisation was required in 10% (17/176) of patients of which a higher proportion came from the transarterial group (83% v 17%). Despite these findings 60% (106/176) of patients were reported as having a decreasing/stable sac of which a higher proportion came from the transarterial group (64% v 52%). Significantly more complications were reported after transarterial embolisations compared to translumbar (TA 10% v TL 0% P= 0.04).

Three studies analysed the outcomes of translumbar and transarterial interventions however they did not report the outcomes of the two interventions separately. Within these studies there were a total of 216 interventions from which 74% (160) were reported to be clinically successful procedures. The largest cohort in this group [183] (95 patients) found freedom from explant, freedom from second embolisation, and freedom from sac expansion was 88.8%, 75.8% and 43.7% respectively at 5 years. Interestingly in this group 51% of patients continued to have sac expansion post intervention. Hyperlipidaemia was the only variable associated with a greater risk of patients requiring a second intervention (HR, 9.64; 95%CI, 2.22-41.86) however there was no association with graft used, embolisation material, number of interventions, or route of access. In addition, no single vessel embolised offered

better protection against secondary intervention or sac expansion. One study [209] reported outcomes for both a transarterial approach and direct sac puncture.

Due to a paucity of outcome data on open/laparoscopic ligation (of aortic side branches) and direct sac puncture, I am unable to perform a formal comparison of these techniques with transarterial or translumbar embolisation. Inclusive of all studies analysed within this review there were 392 interventions from which 111 were unsuccessful (28%).

Discussion

Rupture post EVAR with an isolated type II endoleak appears to be rare. It occurs in less than 1% of all type II endoleaks with a third of ruptures occurring in the absence of known sac expansion. Analysing the most common procedures for the treatment of an isolated type II endoleak together, a third are unsuccessful at occluding the endoleak. This study reveals that 10% of patients develop a type II endoleak post EVAR which is in line with findings by Gelfand *et al*[174] who reported an incidence up to 8% however, others have reported an incidence of type II endoleaks as high as 44%[174,210]. Within this study 32.3% of type II endoleaks were reported to have resolved spontaneously, which is in line with findings by Sheehan *et al*[206] however data regarding spontaneous resolution rates show a significant amount of variability with one study reporting that 80% resolve within 6 months[177].

In this review 14 ruptures associated with isolated type II endoleaks were identified (0.9% of type II endoleaks) however over a third of these ruptures did not have concurrent sac expansion. Wyss T *et al*[176] noted that of four ruptures, all had type II endoleaks with sac expansion however Fransen *et al*[188] found that of 7 ruptures, 3 had known sac expansion while 4 had a stable or shrinking sac size. Jones *et al* found that patients with persistent type II endoleak had a significantly higher rate of sac enlargement (P=0.01), re-intervention (P=0.001), conversion to open repair (P= 0.001) and rupture (P= 0.03) however, Van Marrewijk *et al*[161] in his review of the EUROSTAR data found no correlation between type II endoleaks and risk of late rupture. This review finds an unclear picture of the risk of sac expansion in patients with type II endoleaks, and highlights concerns regarding the current use of sac expansion as a surrogate marker for risk of rupture.

The most common criteria for treatment of a type II endoleak in this review was a persistent type II endoleak or associated sac expansion above a threshold of 5mm, however criteria for intervention varied significantly between studies. Growth of more than 5mm has been shown to represent an actual change in aneurysm size rather than a measurement error[211] however intervention at this point does not appear to be evidence based. Current guidelines are that a conservative approach is appropriate for type II endoleaks without sac expansion. Intervention is recommended for type II endoleaks with increased sac diameter ≥10 mm, with conversion to open surgery in case of failure (level 2b) [212].

The most common intervention for treating isolated type II endoleaks is a transarterial embolisation which routinely involves a percutaneous transfemoral or transbrachial approach, with the aim of selectively catheterising the nidus of the endoleak via its collaterals. This approach is feasible in treating a type II endoleak arising from the inferior mesenteric artery (IMA) if there is a clear transarterial path from the superior mesenteric artery to the IMA via the middle colic and marginal arteries. In this study the transarterial approach had a failure rate of 37.5%. Translumbar embolisations involve placing a needle through the retro-peritoneum at the level of the endoleak and advancing under direct fluoroscopic guidance, anterior to a vertebral body to access the aneurysm sac. This procedure is most commonly performed from the left side of the patient to avoid the inferior vena cava (IVC), with CT images used to determine the optimum entry point, angle and depth for sac puncture; however it has been performed from the right in a technique that traverses the IVC[213]. In this study the translumbar approach had a failure rate of 19%. Analysing these approaches separately a translumbar approach has a higher success rate (TL 81% v TA 62.5% P = 0.02) with a lower risk of complications (TA 10% Vs TL 0% P= 0.04).

Direct sac puncture and laparoscopic ligation have also been described to treat type II endoleaks however were not formally analysed in this review due to a lack of comparable outcome data. Direct sac puncture involves placing the patient in a supine or prone position and inserting a needle under CT and fluoroscopic guidance directly into the aneurysm sac at the site of the suspected endoleak. Despite its similarity to the techniques used in translumbar embolisation, both have been described separately in the literature. No large case series exist for this technique however Uthoff *et al* [214]recently reported 21 direct sac punctures for type II endoleaks with a 50% recurrence rate, 1 graft perforation and 1 pulmonary embolism secondary to incidental extravasation of glue in the right lateral aspect of the inferior vena cava. In addition one study [209] reported outcome data from both a transarterial approach and direct sac puncture however did not report the outcomes separately.

Several successful case reports [215-217],[218] exist regarding the open/laparoscopic treatment of type II endoleaks by ligation of lumbar and/or inferior mesenteric arteries however no large case series has been published. The 'sacotomy' technique was first proposed in a case report by Hinchcliffe *et al* in 2002[219] who described a midline laparotomy to expose the aneurysm sac which was subsequently opened. Any bleeding vessels were oversewn with Prolene suture before the sac was then closed with absorbable suture without the need for aortic clamping. All reports have suggested that laparoscopic ligation is a safe minimally invasive alternative however one study[220] reported performing a redo laparoscopic ligation of a patent IMA due to it being missed at the primary operation.

This analysis reveals that despite intervention a large number of patients do not have a stable or decreasing sac. This finding is in keeping with previous studies for example Aziz *et*

al [207]found that regardless of the approach, intervention does not appear to appreciably diminish aneurysm growth. Despite these findings, a lack of post embolisation ruptures which was similarly seen in this review may suggest that by decreasing perfusion to the previously expanding sac, the sac stabilises and its risk of rupture reduces[161]. This suggests that an inability to eradicate a leak may not necessarily equate to clinical failure.

Poor outcomes from embolisations of type II endoleaks have been explained by comparing type II endoleaks to arterial malformations which recruit nearby vessels over time. It has been suggested therefore that single vessel embolisation is ineffective. Kasirajan *et al*[198] noted that failure was often the result of being unable to reach and coil the aneurysm sac and that in 5 out of 6 patients where this was possible, the endoleak was treated successfully. This suggests that the most important aspect of embolising type II endoleaks is gaining access to the aneurysm sac rather than the approach taken.

There are several limitations within this study. The studies were all retrospective in nature with no randomised controlled trials. Some studies had small patient numbers however by combining these we have reported on 21,728 patients post EVAR and 392 interventions for the treatment of type II endoleaks. There was marked variability in length of follow up between studies with the longest being 4.8 years and this heterogeneity within the available data makes it difficult to perform further statistical analysis. Further research should include a long term prospective study to define the natural history of type II endoleaks including randomised controlled trials of different approaches to the treatment of type II endoleaks and of available embolic agents. Currently there is a lack of outcome data regarding the open/laparoscopic techniques to treating type II endoleaks and direct sac punctures. Ideally a central registry should be kept of outcomes of interventions to treat type II endoleaks to

enable a large accurate analysis to be performed of techniques of intervention. A randomised controlled trial comparing intervention to no intervention is also necessary, to determine a consensus regarding the criteria for intervention. In addition further research is needed to find a more effective screening tool to identify patients at risk of rupture for example biomarkers.

Summary

1. **Type II endoleak occur in 10% of patients post EVAR**
2. **Rupture post EVAR secondary to an isolated type II endoleak is rare (0.9%)**
3. **A third type II endoleaks spontaneously resolve**
4. **A third of endovascular interventions were not successful at embolising the endoleak**

4.4 Type II endoleak: Outcomes from a single centre

As described earlier, type II endoleak is the most common type of endoleak and no gold standard treatment strategy currently exists[221]. The decision to intervene is often down to surgeon preference and although vascular centres that do not routinely attempt to abolish type II endoleaks (with or without sac expansion) have reported good outcomes[182], other centres aim to embolise all type II endoleaks, with or without evidence of sac expansion. I aimed to examine the incidence and outcomes of type II endoleak, at a single institution that conservatively manages patients with type II endoleak.

Methods

Within this study, 904 consecutive patients who underwent EVAR for AAA between September 1995 and July 2013 at the Leicester Royal Infirmary were entered onto a prospective database. This data was collected pre-operatively from patients in a face to face meeting where each respective patient was asked about their co-morbidities. Where data was not available electronically it was sourced from each respective patient's notes. EVARs were performed by a dedicated vascular team with choice of endograft being dependant on arterial morphology and operator preferences. Collected data included preoperative patient demographics for example the presence of co-morbidities (smoking, diabetes, chronic renal failure, ischaemic heart disease, hypertension and cerebrovascular disease), pre-op aneurysm diameter and intraoperative details.

Following EVAR, patients were followed up at regular outpatient appointments with clinical examination and duplex ultrasound scan (DUSS) at 1, 3 and 6 months postoperatively, and at 6-monthly intervals thereafter. At the time of DUSS, data were recorded on sac size, including the presence or absence of endoleak. Computed tomography (CT) scans were

performed as necessary to confirm or clarify complications detected by DUSS. All outcomes including the presence of endoleak, stent migration, stent kinking, conversion to open surgical repair, rupture and death were recorded prospectively on a research database. Those patients in whom DUSS was not possible due to large body habitus were followed up with yearly CT scans with data as above recorded.

Currently DUSS is performed by a trained vascular technician using a GE Logiq E9 scanner (Fairfield, USA) with a C1-5 MHz broadband curved array transducer (B-mode imaging, colour flow imaging and spectral Doppler modalities). Over the study period this centre has also used a Philips Medical Systems HDI 5000 duplex ultrasound scanner (Bothell WA, USA) with a C5-2 MHz broadband curved array transducer (B-mode imaging, colour flow imaging and spectral Doppler modalities). B-mode imaging of the aneurysm sac was performed in transverse and longitudinal planes to identify the graft and to examine the sac contents. The maximum sac diameter (outer wall to outer wall) was measured in both antero-posterior and lateral planes (side to- side diameter from the coronal position) and any changes in sac size were determined. Outer wall to outer wall diameter measurements have recently been demonstrated to have a high repeatability and reproducibility[222]. Colour flow imaging was the principal method used to examine the sac for evidence of endoleak. The colour flow scanner controls were also optimised to detect low-velocity flow from very small endoleaks. Spectral Doppler recordings were taken from any endoleak to examine flow characteristics (pendulum flow suggesting a blind-ending endoleak, or directional flow that might suggest both inflow and outflow). Type II endoleak was defined as blood flow outside of the stent graft, but within the aneurysm sac, caused by retrograde filling from aortic side branches. Patients with inflammatory or infective aneurysms were excluded from this study.

The primary analysis performed aimed to compare those with type II endoleak *versus* a group with no post EVAR complications by excluding all patients who died within 30 days of EVAR and those who developed other complications of EVAR for example endoleak (other than type II endoleak), graft migration and graft kinking. These patients were excluded to enable a direct comparison of patients with type II endoleak (who also had no other complication of EVAR) against patients who had not developed any other complication of EVAR. This was in an attempt to not bias the group without type II endoleak in favour of worse outcomes.

A subgroup analysis aimed to compare outcomes in those with type II endoleak against those without type II endoleak. The no type II endoleak group included patients who died within 30 days of EVAR and those who developed other complications of EVAR for example endoleak (other than type II endoleak), graft migration and graft kinking. Dangerous / life threatening complications of EVAR were recognised at follow up and treated urgently to prevent death and all type I endoleaks detected in clinic were admitted with a view to inpatient treatment. Any type I endoleak detected on completion angiogram was treated at the first operation. The primary outcome measures were all cause mortality, aneurysm related mortality and freedom from aneurysm growth. Separate analyses were performed in patients with more than 5mm of sac expansion (compared to original sac size) and those with more than 10mm of sac expansion (compared to original sac size). Secondary outcomes included spontaneous resolution of the endoleak, defined as no visible type II endoleak on two consecutive DUSS with no intervention having been performed.

Statistical analysis

Patients were analysed separately according to the presence or absence of a type II endoleak. Those with type II endoleak were further classified according to the nature of type II endoleak including: - early (first imaged on initial post EVAR DUSS), late (first imaged more than twelve months after EVAR) and persistent (present for more than six months). Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) depending on the variance, and were analysed by Fishers exact or Mann-Whitney U test where appropriate. Kaplan Meier analysis was used to estimate all-cause mortality survival rates and freedom from aneurysm sac growth rates with log-rank analysis used to test the equality of survival distributions between different factors. Censoring occurred on the last date that a patient was known to be alive or had attended an outpatient appointment if lost to follow up. Survival and date of last appointment was determined by examining each respective patient on an in house database held at the Leicester Royal Infirmary. Those patients who were recorded as alive and had not attended for their routine EVAR follow up in over 2 years were recorded as lost to follow up.

Cox proportional hazards regression was used to test for independent associations with risk of type II endoleak, sac expansion and all-cause mortality with results expressed as odds ratios (OR) and confidence intervals (CI). Backwards stepwise selection of the following covariates was performed; age, sac diameter, ischaemic heart disease, hypertension, diabetes, cerebral vascular disease, hyperlipidaemia, chronic renal failure, current smoking and gender. All statistical analyses were performed using SPSS v.20 (IBM Corp, Armonk, NY) and assumed to be significant if P-value ≤ 0.05.

Results

During the study period 904 consecutive patients underwent EVAR. From these 904 patients, follow up data was available on 773 patients who were included into the analysis (Data completeness 86%) from which 175 (19%) patients developed type II endoleak (Table 4.5). The majority of missing data was from the early part of data collection 1995-2000 so may represent a learning curve with regard to departmental data collection policies. No differences could be seen in the baseline characteristics of those patients lost to follow up compared to those included within the analysis. Median follow up was 4.1 years (1.8 to 6.2 years) in the no complication group and 3.6 years (1.5 to 5.9 years) in the type II endoleak group. No significant differences were found in preoperative demographics between the two groups. Within the group who developed type II endoleaks (Table 4.6), 59 developed early type II endoleak, 53 developed late type II endoleak and 81 developed persistent type II endoleak. Within the persistent type II endoleak group were 31 late type II endoleaks and 26 early type II endoleaks.

Spontaneous resolution of the endoleak occurred in 95 (54.2%) of all type II endoleaks after a median of 0.63 years (3 months to 1.2 years). Comparing the rate of spontaneous resolution between different types of endoleak, there appears to be a higher rate of spontaneous resolution within the early endoleak group (78%) compared to the late and persistent type II endoleak groups (53% *versus* 53%). Furthermore, the early endoleak group appear to spontaneously resolve earlier (3.12, 1.5 to 11.3 months) compared to the late (1.04 years, 0.6 to 2.2 years) and persistent (1.3 years, 0.9 to 2.2 years) groups respectively. Type II endoleak rates were comparable regardless of the type of endograft used (Table 4.7). Cox regression analysis adjusted for covariates (age, sac diameter, ischaemic heart disease,

hypertension, diabetes, cerebral vascular disease, hyperlipidaemia, chronic renal failure, current smoking and gender) failed to identify any significant associations with the risk of developing type II endoleak.

Table 4.5 - Baseline Characteristics of patients with and without type II endoleak, Continuous data are shown as the mean ± standard deviation and categoric data are shown as number (%)

	Type II endoleak ***n* = 175**	**No Type II endoleak** ***n* = 598**	**P**
Follow up (years)*	3.6 (1.5-5.9)	4.1 (1.8-6.2)	
Age (Years)	74.9 ± 6.6	74.0 ± 8.4	0.1
Spontaneous Resolution	95 (54.2)	-	
Time to resolution (years)*	0.63 (0.25-1.2)	-	
Male	157 (89.7)	553 (92.5)	0.3
Aneurysm Diameter (mm)	64 ± 11	63 ± 10	0.5
Hypertension	70 (40)	254 (42.5)	0.6
Ischaemic Heart Disease	55 (31.4)	183 (30.6)	0.8
Hyperlipidaemia	63 (36)	210 (35.1)	0.8
Diabetes	18 (10.3)	63 (10.5)	1.0
Chronic Renal Failure	6 (3.4)	33 (5.5)	0.3
Cerebrovascular disease	11 (6.3)	41 (6.9)	0.9
Smoking	95 (54.3)	334 (55.9)	0.7

*Median and IQR

Table 4.6 - Baseline Characteristics of patients with different classifications of type II endoleak, Continuous data are shown as the mean and standard deviation and categoric data are shown as number (%).

	Early type II endoleak *n* = 59	**Late type II endoleak *n*=53**	**Persistent type II endoleak *n*= 81**
Median follow up (years)*	3.7 (1.7-5.6)	5.6 (3.6-8.6)	5.1 (2.5-7.3)
Age (Years)	75.3 ± 7.4	74.8 ± 6.7	74.4 ± 6.6
Male	52 (88.1)	43 (81.1)	71 (87.7)
Aneurysm Diameter (mm)	64 ± 11	66 ± 12	66 ± 1.2
Spontaneous resolution	46 (78)	25 (47.2)	43 (53)
Time to resolution (years)*	0.26 (0.13-0.94)	1.04 (0.6-2.2)	1.3 (0.9-2.2)
Hypertension	23 (39)	15 (28)	33 (40.7)
Ischaemic Heart Disease	15 (25)	9 (17)	19 (23.4)
Hyperlipidaemia	13 (22)	13 (24.5)	25 (30.9)
Diabetes	5 (8.5)	4 (7.5)	8 (9.9)
Chronic Renal Failure	1 (1.7)	0 (0)	1 (1.2)
Cerebrovascular disease	1 (1.7)	3 (5.6)	9 (11.1)
Smoking	29 (49.1)	20 (37.7)	44 (54.3)

* Median and inter quartile range

Table 4.7 - Type II endoleak distribution by device models

Device	Type II endoleak *n* = 175	No Type II endoleak *n* = 598	P
Cook Zenith	91	304	0.8
Cook Trifab	15	52	1.0
Medtronic Endurant	18	54	0.6
Talent	18	57	0.6
Anaconda	2	14	0.5
Gore Excluder	24	79	0.9
Edwards Lifepath	2	2	0.2
Cook Uni Iliac	-	9	-
Local Device	-	5	-

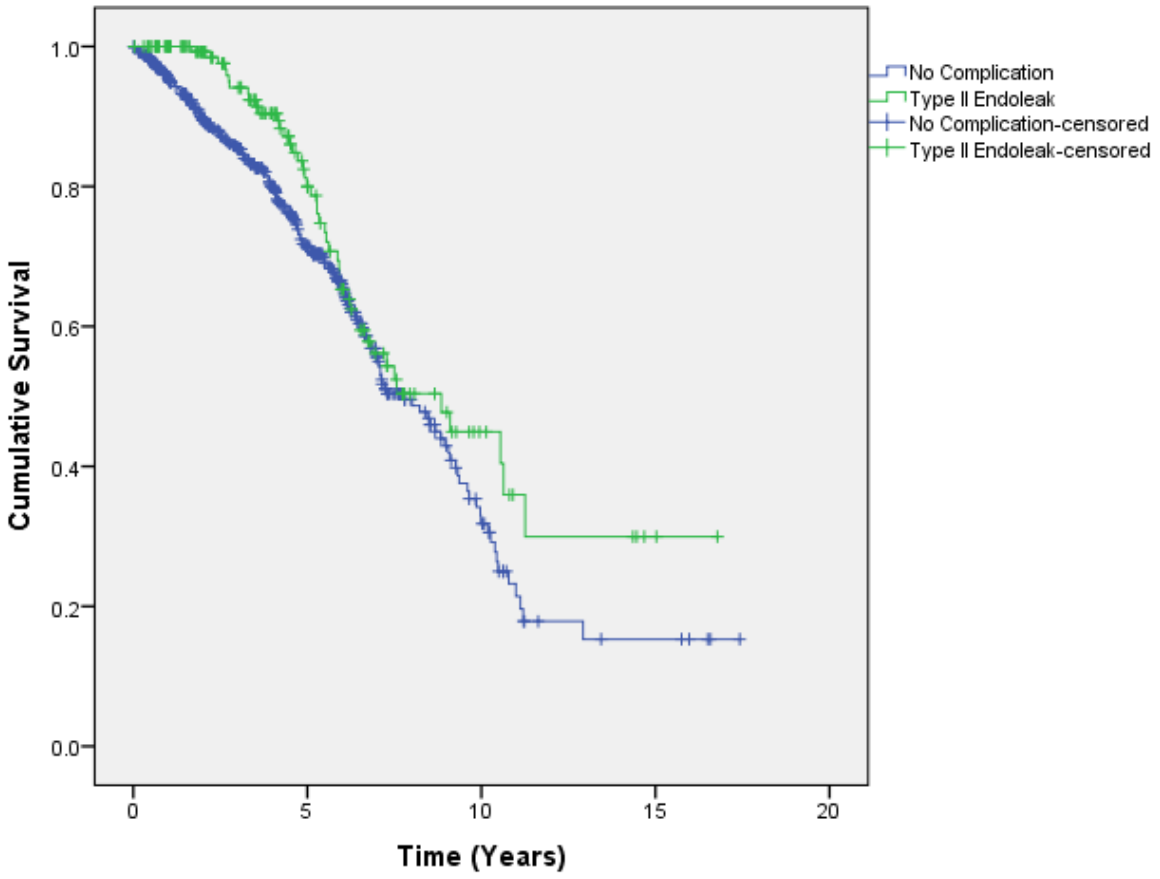
The association of type II endoleak with type I endoleak.

Within the study period 27 patients developed type 1 endoleak, 6 of which had a type II endoleak. Three of these patients had a persistent and late type II endoleak from which 2 developed 10mm of sac expansion. One patient had a persistent type II endoleak and no sac expansion and 2 patients had type II endoleak with no sac size changes. 31 patients had both a persistent and late type II endoleak from which only 3 developed a type I endoleak. Six type I endoleaks occurred in patients who had had a type II endoleak (3.4%) whilst twenty one type I endoleaks (3.5%) occurred in patients who had not had a type II endoleak therefore this data demonstrates no association between type II endoleak and the development of a type I endoleak (P = 1.0).

All cause and aneurysm related survival

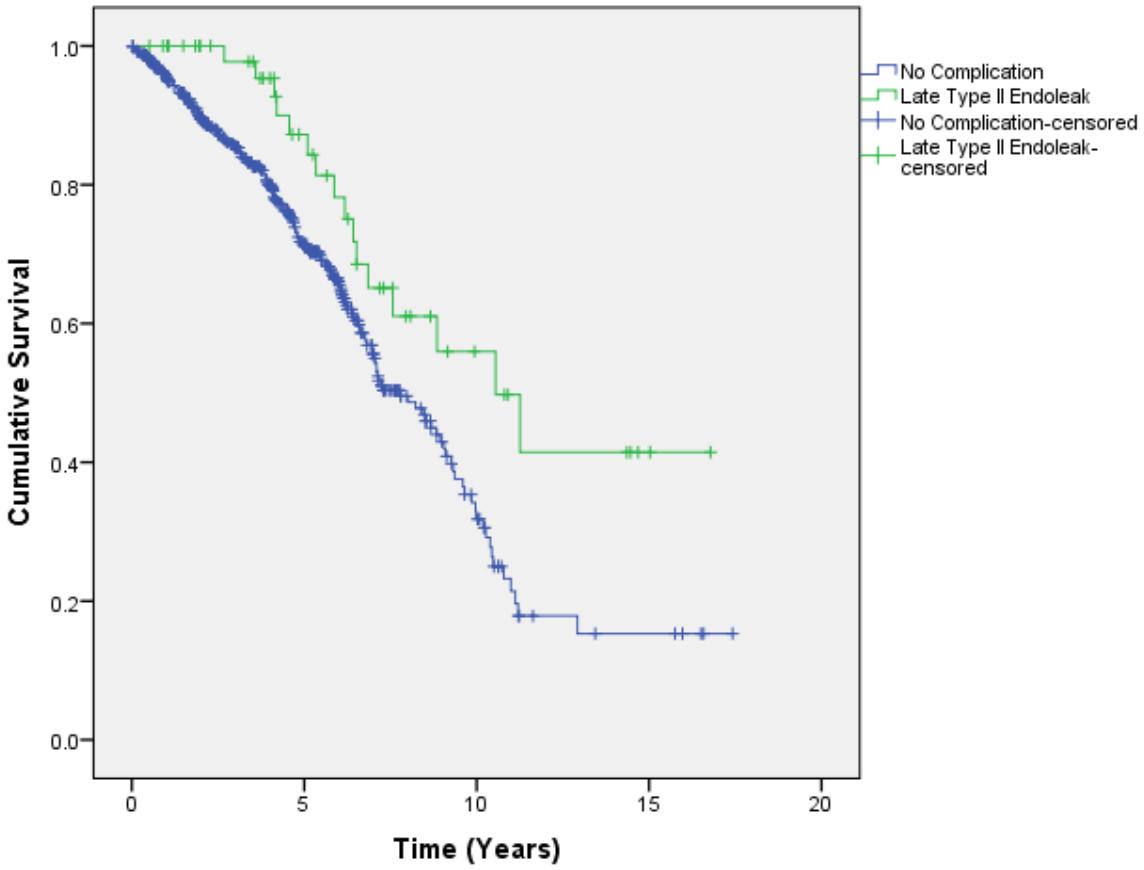
Analysis of patients with type II endoleak *versus* a post EVAR, no complication group demonstrated an improved all cause survival in patients with type II endoleak compared to those with no complication; 94.1% *versus* 85.6% at 3 years and 80% *versus* 71.4% at 5 years (P = 0.04), a finding which persists out to 9 years; 47.7% *versus* 41.9% (Figure 4.4). This remained significant when including patients with known complications into the non-type II endoleak group; 94.1% *versus* 85.3% at 3 years which perseveres out to 9 years: 47.7% *versus* 40.4%; P= 0.01. Analysing all-cause mortality within the different classifications of type II endoleaks, those with late endoleaks appear to have a significant survival advantage compared to those with no complication (Figure 4.5); 97.7% *versus* 85.6% at 3 years which persists out to 9 years; 56% *versus* 41.9*%*, P = 0.008. This again remained significant when including patients with known complications into the analysis; 97.7% *versus* 86.3% at 3 years and 56% *versus* 41.4*%* at 9 years (P = 0.004) over those without type II endoleaks. Analysing all cause survival in patients with persistent and early type II endoleak *versus* those with no complications demonstrated no difference in all-cause mortality (Figure 4.6a/b).

Figure 4.4 - Kaplan Meier analysis comparing cumulative all cause survival in patients with type II endoleak *versus* those with no complication. Log Rank (Mantel Cox), P = 0.04.



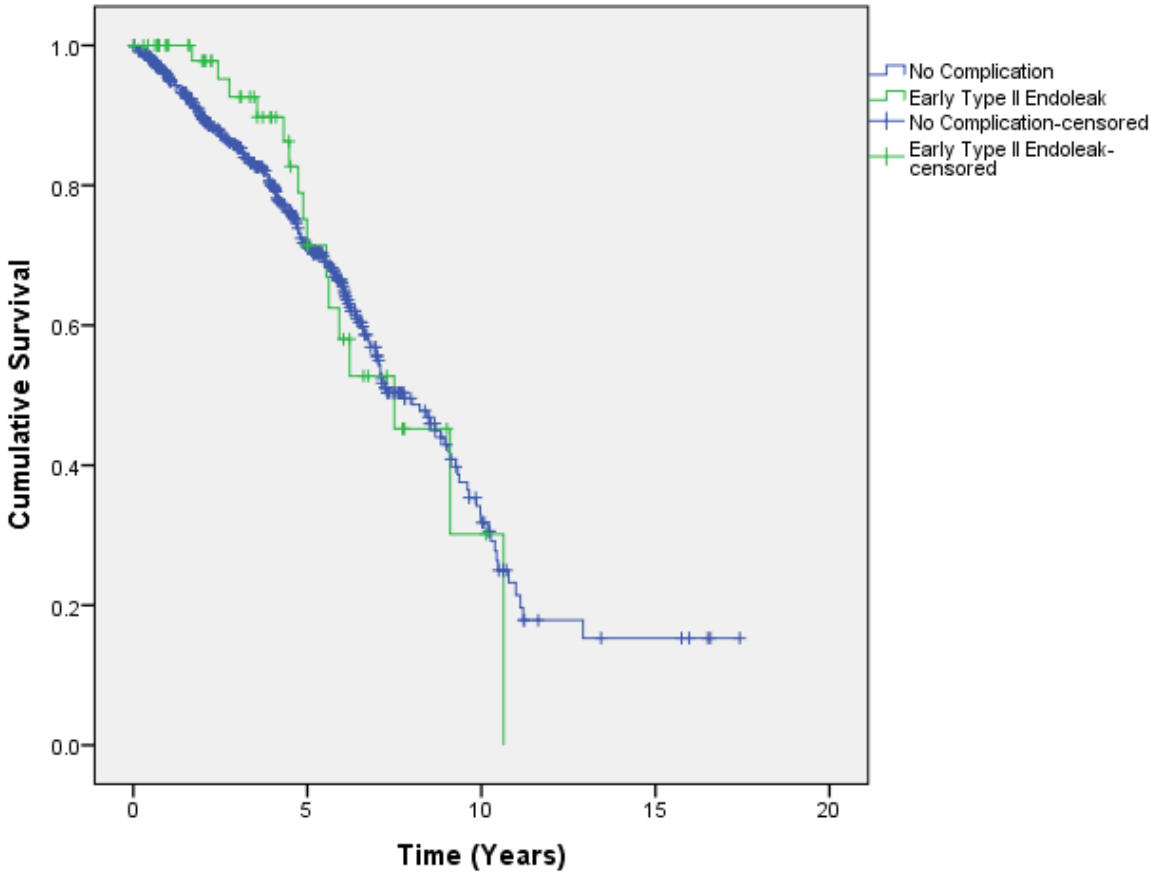
	Years	0.5	1	3	5	7	9
No Complication	n at risk	531	472	334	197	87	40
	Survival %	98.0	95.5	85.6	71.4	55.6	41.9
Type II Endoleak	n at risk	158	143	108	64	31	17
	Survival %	100	100	94.1	80	56.2	47.7

Figure 4.5 – Kaplan Meier analysis comparing cumulative all cause survival in patients with a late type II endoleak (visualised after one year of follow up) *versus* those with no complication. Log Rank (Mantel Cox), P = 0.008.



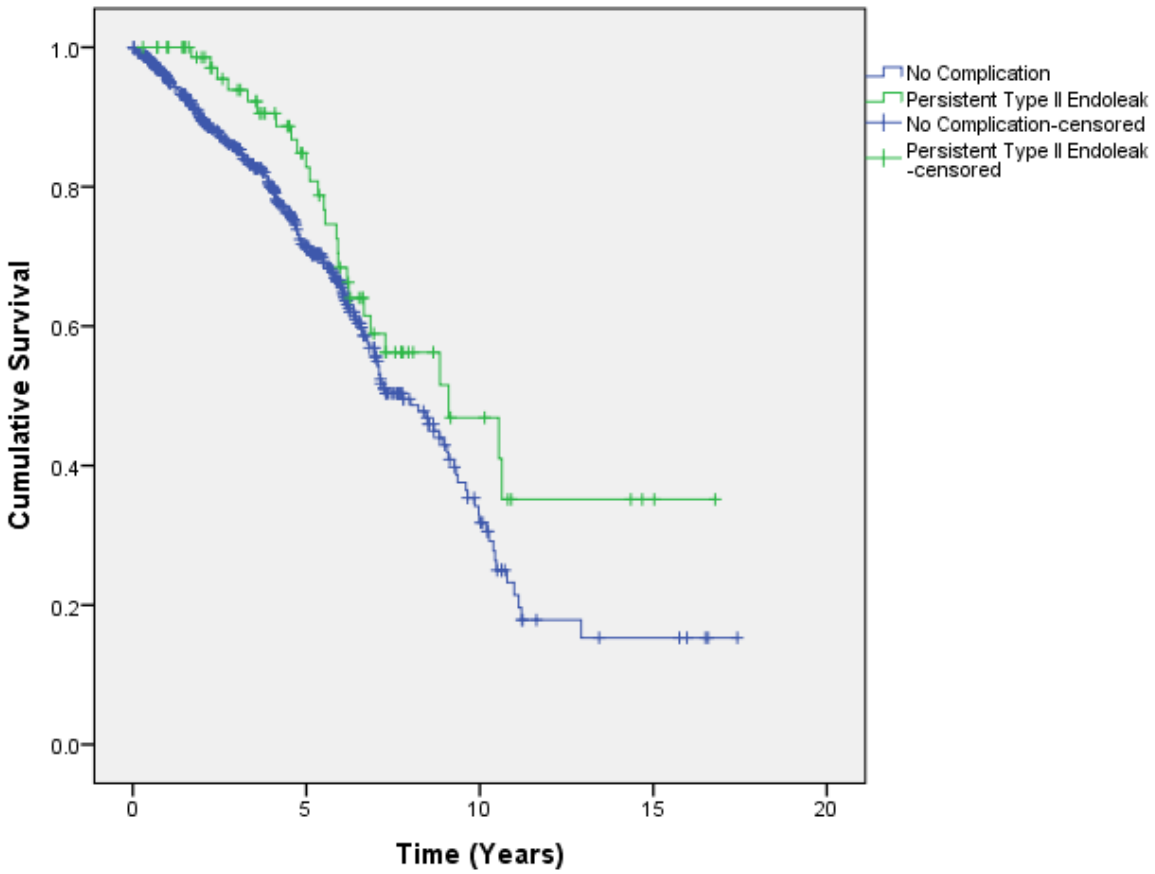
	Years	0.5	1	3	5	7	9
No Complication	n at risk	530	472	334	197	87	40
	Survival %	98.4	95.5	85.6	71.4	55.6	41.9
Type II Endoleak	n at risk	52	50	43	29	18	10
	Survival %	100	100	97.7	84.3	65.1	56.0

Figure 4.6a – Kaplan Meier analysis comparing cumulative all cause survival in patients with an early type II endoleak (visualised on first follow up) *versus* those with no complication. Log Rank (Mantel Cox), P = 0.06.



	Years	0.5	1	3	5	7	9
No Complication	n at risk	531	472	334	197	87	40
	Survival %	98.0	95.5	85.6	71.4	55.6	41.9
Type II Endoleak	n at risk	56	47	35	18	7	3
	Survival %	100	100	92.6	71.4	52.7	45.2

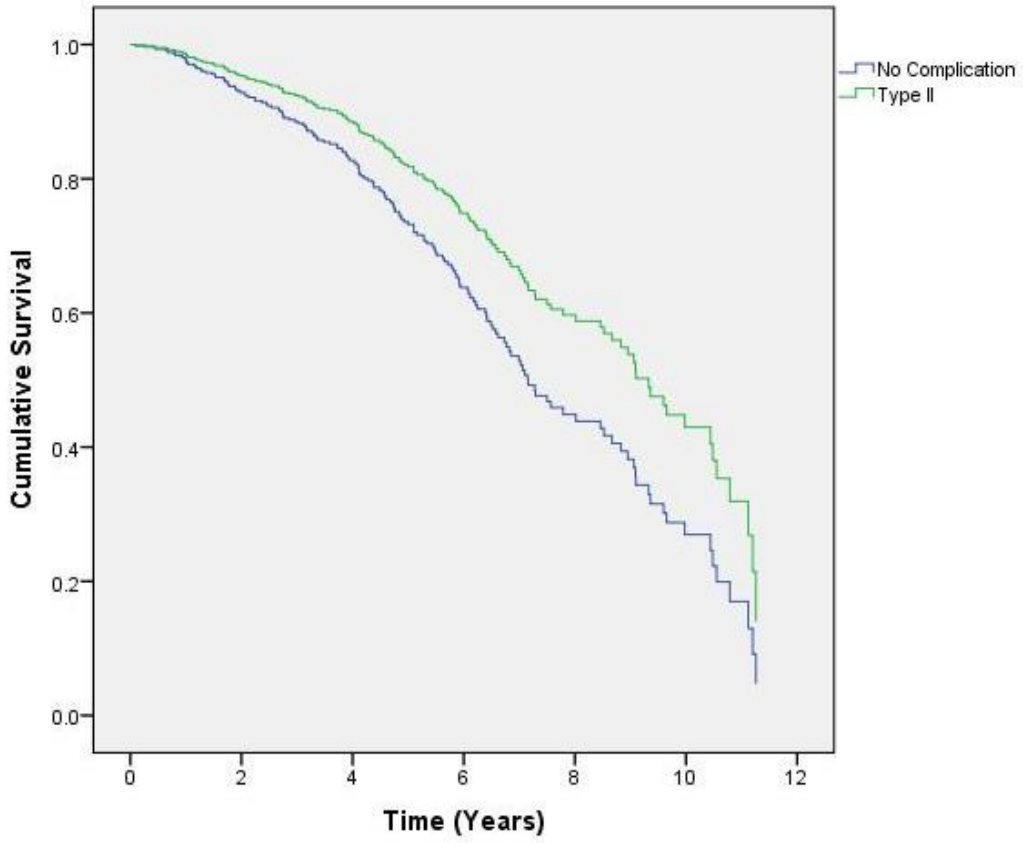
Figure 4.6b – Kaplan Meier analysis comparing cumulative all cause survival in patients with a persistent type II endoleak (More than six months) *versus* those with no complication. Log Rank (Mantel Cox), P = 0.8.



	Years	0.5	1	3	5	7	9
No Complication	n at risk	531	472	334	197	87	40
	Survival %	98	95.5	85.6	71.4	55.6	41.9
Type II Endoleak	n at risk	80	75	58	40	21	10
	Survival %	100	100	93.9	80.8	56.2	46.9

After adjustment using a backwards, stepwise cox Regression with the Kaplan Meier curve adjusted for covariates including age, aortic diameter, ischaemic heart disease, cerebrovascular disease, diabetes, renal failure, hyperlipidaemia and smoking, type II endoleak remained significantly associated with improved survival (Figure 4.7, P=0.027). In addition age at EVAR (P=0.0001) and aortic diameter (P=0.0001) were both significantly associated with all-cause mortality. After adjustment for comorbidities, Early (P=0.208), Persistent (P=0.126) and late type II endoleak (p=0.087) lose their significant association with all-cause mortality. This may suggest that patients with type II endoleak have a lower burden of atherosclerotic disease.

Figure 4.7 – Adjusted Kaplan Meier analysis comparing cumulative survival in patients with a type II endoleak *versus* those with no complication.



Aneurysm related mortality

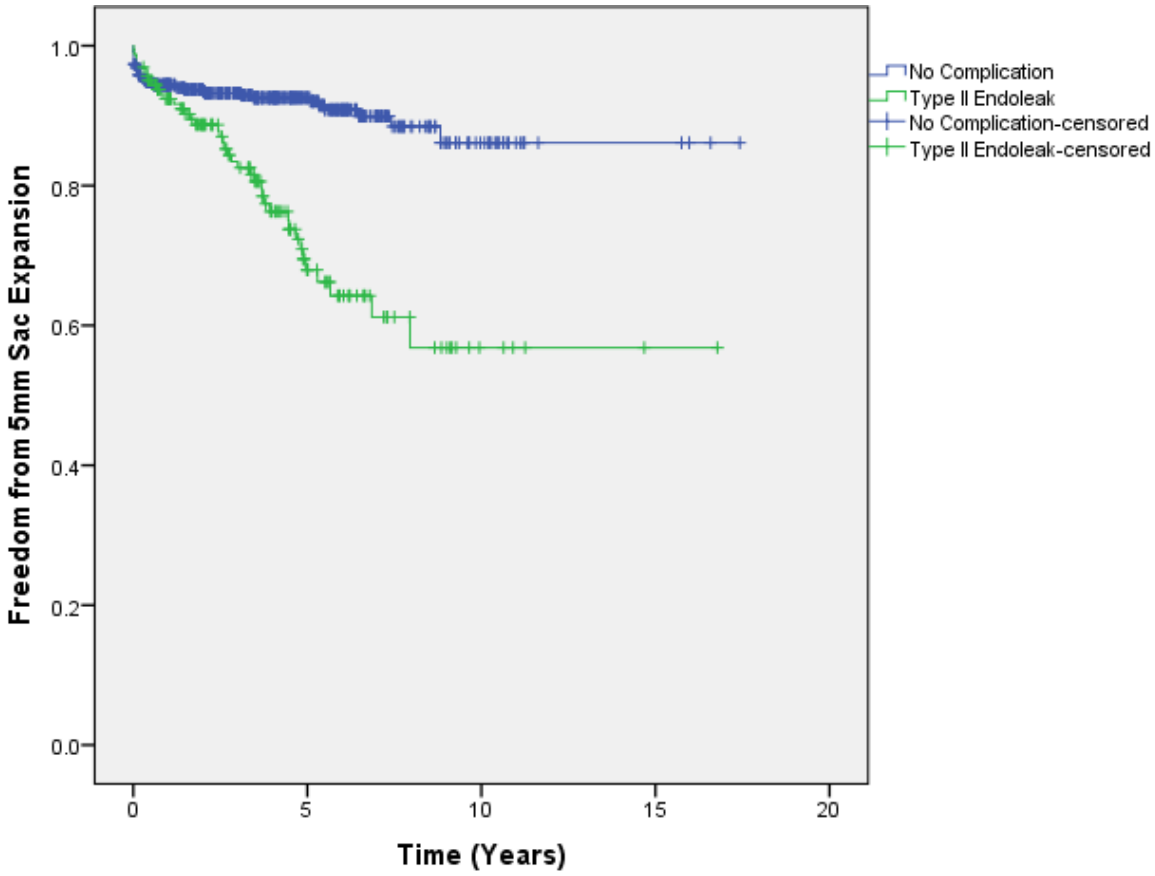
No significant difference was demonstrated between aneurysm related mortality in the group of patients with type II endoleak compared to the group without complication; 98.1% *versus* 100% at five years and 96.8% *versus* 98.3 at seven years (P=0.44). Eleven aneurysm ruptures occurred at a median of 41 months post discharge (IQR 9.5-52.5 months) from which two occurred in the perioperative period and nine occurred after discharge from hospital. One patient was reported to have a type III endoleak and consequently ruptured prior to a bridging stent being placed whilst another patient had a stent strut fracture. One patient who underwent elective EVAR aged 71 for a 90mm AAA, developed a persistent type II endoleak 18 months post EVAR and sac expansion (more than 10mm from original sac size). The type II endoleak was treated conservatively and the patient was admitted with a proximal type 1 endoleak 56 months post EVAR, treated with proximal cuff. At 72 months this patient was admitted with a ruptured AAA and died. No patients with an isolated type II endoleak presented with a ruptured AAA.

Sac expansion

Freedom from sac expansion (an increase of 5mm from pre-operative sac size) was demonstrated to be significantly lower in the group of patients with type II endoleak compared to the group without complication (Figure 4.8) at 3 years (82.5% versus 93.2%), a finding that can be demonstrated throughout the duration of follow up (P = 0.0001). Freedom from sac expansion of more than 10mm from pre-operative sac size, was however comparable between the two groups (Figure 4.9, P = 0.1). Cox regression analysis adjusted for covariates (age, sac diameter, ischaemic heart disease, hypertension, diabetes, cerebral

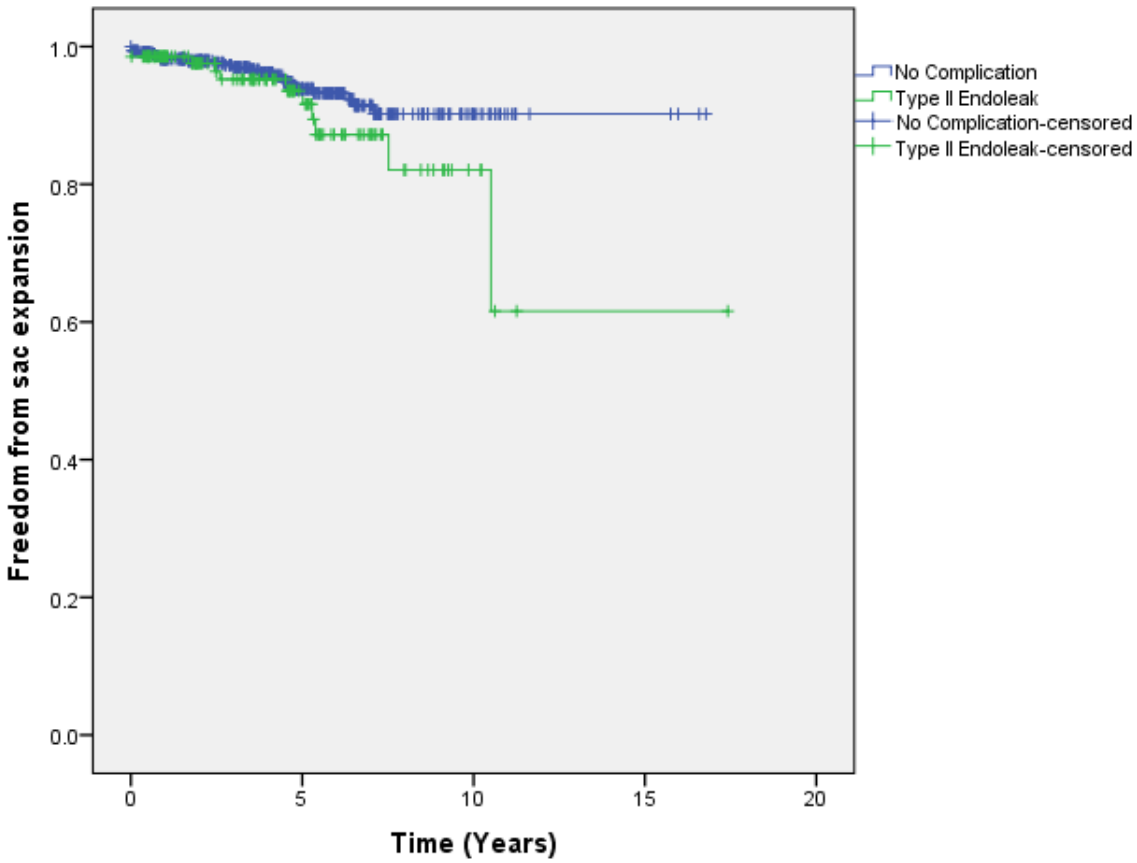
vascular disease, hyperlipidaemia, chronic renal failure, current smoking and gender) confirmed a strong independent association between the presence of type II endoleak and the likelihood of sac expansion (more than 5mm) after EVAR (OR 3.3, 95% CI 1.87-4.91; P = 0.0001) however failed to demonstrate this with sac expansion of more than 10mm (P = 0.1). These covariates were chosen as they each have a well-established association with AAA and increased all-cause mortality.

Figure 4.8 – Kaplan Meier analysis comparing freedom from sac expansion (more than 5mm) in patients with type II endoleak *versus* those with no complication. Log Rank (Mantel Cox), P = 0.0001.



	Years	0.5	1	3	5	7	9
No Complication	n at risk	493	440	301	178	75	32
	Survival %	94.8	94.4	93.2	92.6	89.9	86.1
Type II Endoleak	n at risk	149	133	91	42	19	10
	Survival %	95	92.4	82.5	67.9	61.2	56.8

Figure 4.9 – Kaplan Meier analysis comparing freedom from sac expansion (more than 10mm) in patients with type II endoleak (visualised after one year of follow up) *versus* those with no complication. Log Rank (Mantel Cox), P = 0.1.



	Years	0.5	1	3	5	7	9
No Complication	n at risk	442	400	294	169	77	37
	Survival %	99.2	98.2	97.0	93.9	91.4	90.2
Type II Endoleak	n at risk	128	108	78	47	22	10
	Survival %	98.5	98.5	95.2	91.6	87.2	82.1

Re-intervention post EVAR

Interventions to abolish a type II endoleak were not routinely performed after any specific time period or at any specific sac diameter change thus any decision to intervene was down to surgeon /patient preference. A total of 9 interventions have been performed to embolise a type II endoleak at the Leicester Royal Infirmary (One direct sac puncture and eight transarterial interventions). Seven of these interventions were in patients who had more than 10mm of sac expansion and 3 out of the 9 interventions were clinically successful (defined as no type II endoleak present on repeat DUSS). Three patients underwent repeat re-intervention; one IMA Clipping, one transarterial coil and one conversion to open surgical repair, all of which were successful. The patient who underwent conversion to open repair had a persistent type II endoleak, failed transarterial intervention and sac expansion from 51mm to 77mm. No post intervention major complications occurred.

Discussion

This study demonstrates that the conservative management of type II endoleak is not associated with an increase in the risk of aneurysm related mortality, all-cause mortality, 10mm of sac expansion or type I endoleak. This data therefore suggests that a conservative approach to the treatment of type II endoleak is safe. Only three out of the nine interventions performed to abolish a type II endoleak were successful which is in line with previous data suggesting a high risk of treatment failure[180]. Although no complications were noted after intervention in this study, Haulon *et al*[193] reported a post transarterial intervention, mesenteric thrombosis whilst Uthoff and colleagues[214] reported a pulmonary embolism secondary to leaked embolent and an endograft perforation. The risk of an

aggressive approach (treating all type II endoleaks or those with 5mm of sac expansion) may therefore outweigh any benefit.

In keeping with previous findings[223], Type II endoleak was not associated with an increase in aneurysm related mortality, however, it was associated with an increased survival. Although this data is not the first to note this unintuitive finding[223], no clear explanation currently exists. Previous studies[161,177,224] have demonstrated an association between persistent type II endoleaks and adverse outcomes however this data demonstrated no increase in aneurysm or all-cause mortality in this group of patients.

One explanation for the improved survival demonstrated in those with type II endoleak could be differences in patient demographics. Although no differences were seen between patient co-morbidities in this study, Van Marrewijk *et al*[161] found current smoking and a decreased ankle-brachial index (0.87 or less) to reduce the risk of type II endoleak. El Batti[224] and colleagues similarly demonstrated that the risk of type II endoleak was reduced in active smokers (OR, 0.16 CI, 95% 0.04-0.71; P 0.01) and patients with coronary artery disease (OR, 0.65; CI, 95% 0.45-0.92; P=0 .01). It is plausible that those patients with type II endoleak have less profound atherosclerosis both peripherally and centrally however studies to demonstrate a reduced cardiovascular risk in this group of patients would be required to investigate this.

This study confirms an association between type II endoleak and sac expansion of 5mm, which is in keeping with previous studies[177,224], however, although growth of more than 5mm has been shown to represent an actual change in aneurysm size rather than a measurement error[211], intervention at this point is not evidence-based. Current guidelines from the European Society of Vascular Surgery[212] are that a conservative approach is

appropriate for type II endoleak without sac expansion. Intervention is recommended in the presence of an increased sac diameter of 10mm or more, with conversion to open surgery if endovascular treatment fails (level 2b)[212]. This study failed to show any association between type II endoleak and sac expansion of more than 10mm from pre-operative sac size.

Within this study, 54.2% of all type II endoleaks spontaneously resolved within a median of 7 months. The number of type II endoleaks that spontaneously resolve is variable between studies for example, one study[182] demonstrated that 48% will resolve within 4 years while another[177] suggested that 80% would resolve within 6 months. Taken together these studies suggest that given time, type II endoleak have a reasonable chance of spontaneously resolving, a view which has been confirmed by a systematic review which demonstrated that a third of all isolated type II endoleaks spontaneously resolve up to four years post EVAR[180].

Choice of imaging is likely to affect the reported prevalence of type II endoleak[225],[136]. CT has been reported in some studies to achieve the highest sensitivity and specificity for the detection of endoleak[136], however, in an effort to reduce the cumulative risk of radiation exposure associated with lifelong follow up many vascular centres have evolved to DUSS surveillance with CT only used to confirm suspected complications. Although DUSS surveillance may be a limitation of this study, Schmieder and colleagues[226] recently demonstrated that colour duplex imaging has a higher sensitivity in detecting endoleaks requiring intervention (90% versus 58%)and has a better diagnostic accuracy in identifying the type of endoleak compared to CT which can be improved further by utilising contrast enhanced ultrasound[137]. Contrast enhanced was not utilised during any parts of this study. Gray *et al*[227] demonstrated that colour duplex imaging had a sensitivity of 100% (specificity of 85%) and could replace CT as the first line surveillance tool following EVAR as it was

associated with a reduction in the cost of surveillance without any loss of imaging accuracy. A further limitation of DUSS in general is that it is operator dependant and that its sensitivity can be reduced in patients with a raised BMI[228]. Furthermore, it is possible that some type II endoleaks are misdiagnosed type I or type III endoleak.

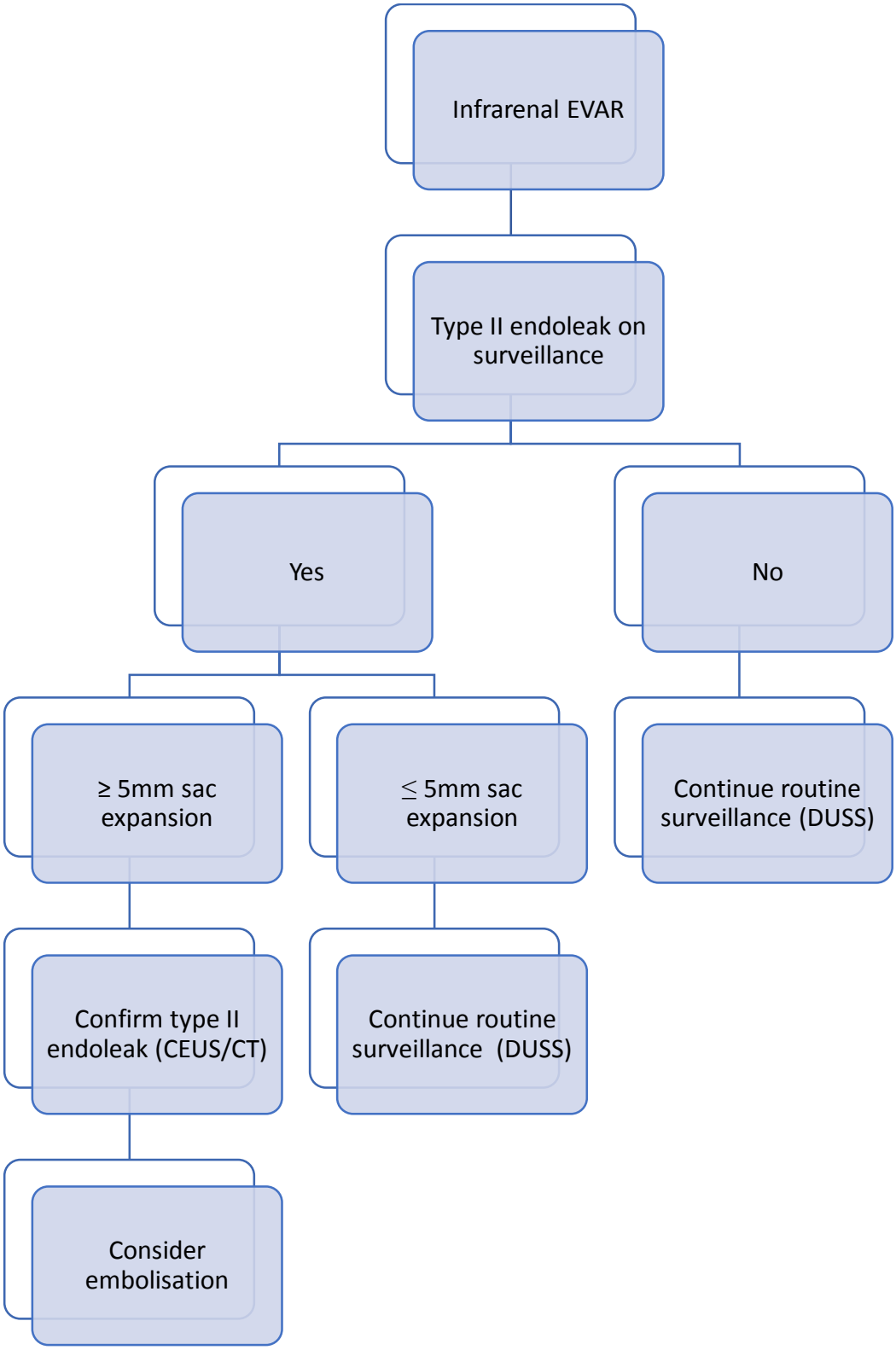
Some studies have suggested that diameter changes post EVAR correlate poorly with volumetric changes which may be more informative. Future follow up may therefore include 3D ultrasound imaging. This study is limited by its retrospective nature however all outcomes including the presence of endoleak, conversion to open surgical repair, rupture and death were recorded prospectively. Not all patients attended follow up (data completeness = 86%) therefore outcome data for some patients is unavailable for analysis, however this study did include data for 773 patients. Within this study, the number of EVAR's performed was heavily weighted towards the more recent years. For example in the year 2000, 23 EVAR's were performed whilst in 2012, 98 EVAR's were performed. This reflects the increasing use of EVAR with time, but skews the follow up times achieved. Although the results of this study appear to highlight an improved all cause survival in a group of patients with type II endoleak post EVAR, this association does not suggest that type II endoleak or growth of the aneurysm post EVAR is desirable.

A limitation of type II endoleak reporting in general is the varying definitions used by authors when referring to early, late and persistent type II endoleaks. A classification system for reporting type II endoleaks is necessary to enable standardisation of reporting and comparison of results. Another limitation of this study is that some patients were treated for their type II endoleak from which the majority had more than 10mm of sac expansion. It is plausible that these patients if left untreated would have gone on to rupture and thus

although this data suggests that a conservative approach in the absence of sac expansion (more than 10mm) appears to be safe, the selective management of those with significant sac expansion may be necessary.

Suggested Algorithm for the management of type II endoleak

Figure 4.10



Summary

1. **19% of patients developed type II endoleak which was higher than identified within the literature review.**
2. **54% spontaneously resolved within a median of seven months**
3. **No association with type I endoleak**
4. **No increase in aneurysm related mortality**
5. **A conservative approach appears to be safe in the absence of significant sac expansion.**

Chapter 5: Potential Biomarkers of type II endoleak

5.1– A systematic review, meta-analysis and meta-regression

Reduction of post EVAR aneurysm related mortality depend largely on the early detection and elective repair of identified complications such as type II endoleak with significant sac expansion. One possible strategy to reduce the cost of surveillance may be to use a two-stage approach using a cheaper high-sensitivity diagnostic test such as biomarkers, followed up with a high-specificity test such as ultrasound. Many studies have investigated the systemic and local levels of biomarkers in patients with AAA, often with conflicting results. However, few[229],[230,231] have focused on biomarkers of complications of EVAR such as endoleak.

Several studies have shown that circulating markers of haemostasis are elevated in patients with aortic ameurysm[232]. The nearly consistent presence of a non-occlusive mural thrombus[11] in patients with AAA, characterized by erythrocyte haemagglutination and neutrophil trapping, a process that releases free haemoglobin, leading to platelet activation, fibrin formation and binding of plasminogen causing oxidative and proteolytic injury of the arterial wall[233] may drive this coagulopathy. This activity is mainly orchestrated at the intraluminal thrombus–blood interface which remains patent in patients with endoleak [234] and thus circulating markers of this activity could be measured peripherally. The aim of this review was to identify potential biomarkers of endoleak that could be useful as markers of type II endoleak and sac expansion.

Methods

Eligibility criteria and study selection

Study titles and abstracts were searched according to PRISMA guidelines[235] by DS and PWS using Medline and Embase databases through OVID Online (Version: OvidSP_UI03.04.02.112, Ovid Technologies, Inc.) in February 2013. No language restrictions or filters used to restrict study designs were applied. Reference lists were searched for further studies to be included. The review was performed using the search terms "Aneurysm AND abdominal AND aortic AND coagulation" NOT "thoracic". DS and PWS, individually reviewed potential studies according to a set of eligibility criteria, with discrepancies discussed. Inclusion criteria were that the study must either a) be an original publication with either a case control design comparing markers of haemostasis in patients with AAA and controls or, b) test the association between markers of haemostasis and aneurysm size.

Study selection and data extraction

Studies included within this analysis were either case-control studies, or studies comparing biomarker levels to aortic diameter. Data extracted included mean or median and standard deviation (SD), interquartile range (IQR), range, standard error of the mean (SEM), 95% confidence intervals (CI), and/or a P value. In addition, the following data were extracted for each article; year of publication, author, journal, and mean aneurysm diameter.

Statistical analysis

We conducted a meta-analysis of summary statistics from the individual biomarker studies. For each study, data relating to biomarker levels in both the AAA and control groups were used to generate standardised mean differences (SMDs), mean differences (MD) and 95% confidence intervals (CI's) using Review Manager version 5.2[75]. Studies were combined using

the inverse variance method with random effects due to the heterogeneity between studies included, with a P value of <0.05 used to determine significance. Individual circulating biomarkers (measured either in blood, serum or plasma), and aortic tissue studies were analysed separately. Biomarker concentrations were each converted to the same SI unit (depending on the predominant unit for each biomarker), and converted to mean and SD as per the Cochrane Handbook for Systematic Reviews Version 5.1.0 updated March 2011. Standard conversion charts were used to convert mg/dl to nmol/l. For articles reporting the median and interquartile range (IQR), we took the median to be representative of the mean, and divided the IQR by 1.35 to generate the SD. For studies reporting the standard error of the mean (SEM), this was multiplied by the square root of the number of subjects within that group to calculate the SD. For studies reporting 95% CI's the SD was calculated by multiplying the difference between the upper and lower intervals by the square root of the number of subjects within the group, then dividing this by 3.92. In studies where a P value had been given but no SD or IQR or SEM, a SD was calculated from the p value using the standard formula from the Cochrane Handbook for Systematic Reviews Version 5.1.0 updated March 2011. Where studies had reported more than 1 subgroup of patients with AAA, a combined mean and SD was obtained through standard formulae. Between study heterogeneity was analysed using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance or random error[69].

To determine whether biomarker concentrations were associated with AAA diameter, meta-regression was performed using n-weighted linear regression (IBM SPSS Version 20). Biomarker concentrations were compared to the reported mean/median aneurysm size from each study. In cases where biomarker concentrations were reported stratified by AAA

diameter, each size sub-group was entered into the regression as a separate outcome. Where reported diameter was greater than or less than a specified diameter, the specified diameter was used. Where reported diameter was given as a range, the central point of the range was used. Sensitivity analyses were performed by excluding studies with less than 100 patients and recalculating the pooled mean difference (MD) estimates for the remaining studies.

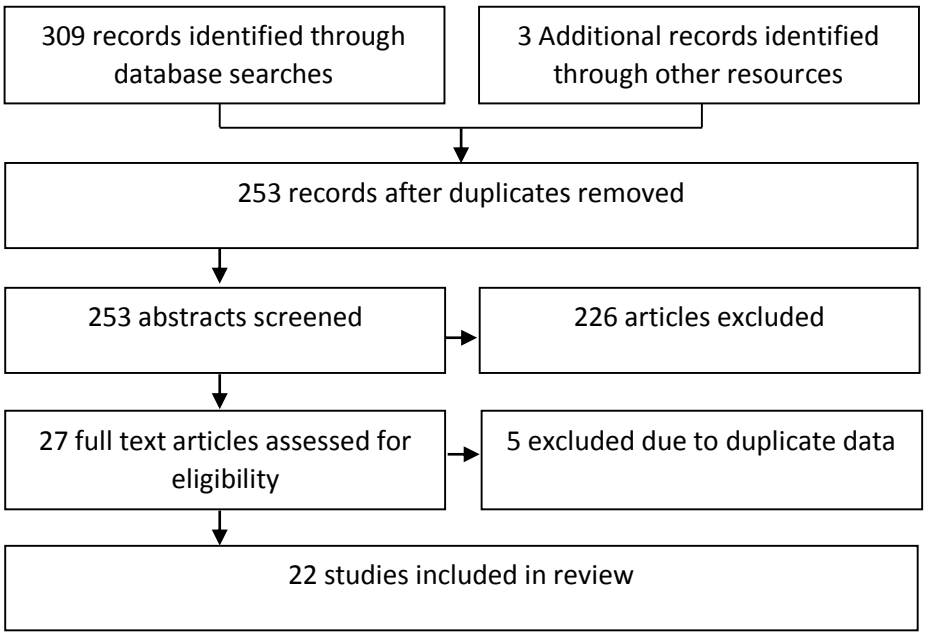
Results

Literature search

A total of 309 abstracts were identified through literature search with 3 studies identified through manual searching of reference lists from these articles. Following removal of duplicates, review of the titles and abstracts of 254 papers was performed. A total of 27 papers were obtained and read in full. Five studies were excluded for the following reasons: Two studies were excluded as they were review articles [233,236], two studies were excluded as they compared markers of coagulation in patients with ruptured versus non ruptured AAA[237,238] and one was excluded as it contained duplicate data[239].

A total of 22 non randomized studies were included in the analysis. Three studies [240,241,242] reported on both a control group of age matched individuals and a control group with peripheral arterial disease. For the purpose of this analysis the peripheral arterial disease group was excluded. Seven studies specifically investigated the association between AAA diameter and markers of haemostasis[243-249]. The PRISMA diagram is shown in Figure 5.1.

Figure 5.1. PRISMA diagram of search



Study Quality and Publication Bias

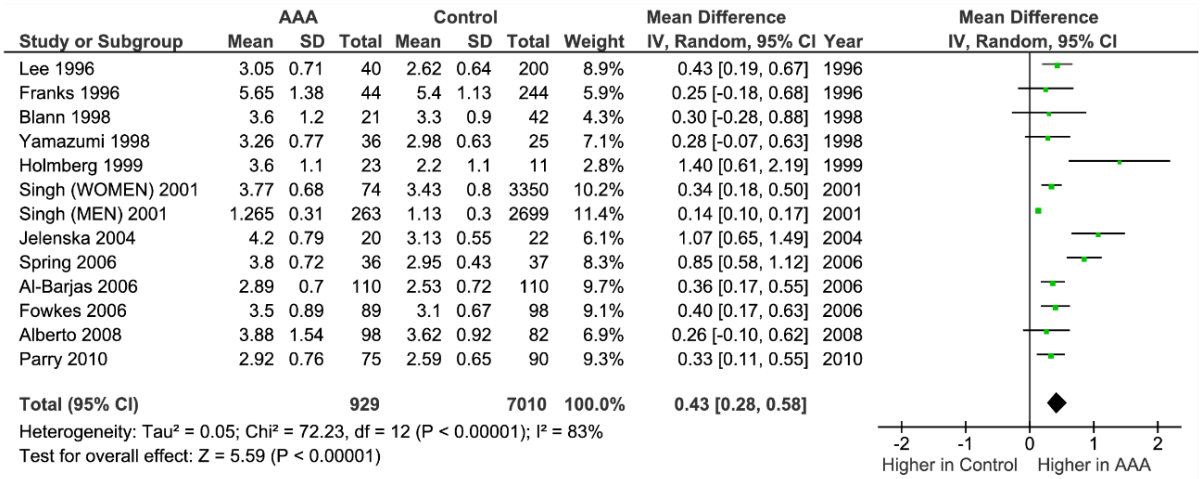
The Newcastle-Ottawa scale was used to assess the quality of non-randomised studies, with all studies scoring 7 or more out of 9. Funnel plots were performed for all outcomes. All funnel plots suggested minimal publication bias.

Fibrinogen

A total of 12 studies [241-243,245,250-255,256] reported on concentrations of plasma fibrinogen in patients with and without AAA. The largest of these studies included 3,424 patients[257] while the smallest contained thirty four[254]. Methods were similar between studies with the majority comparing AAA diagnosed on USS against healthy aged matched controls however two studies utilized control groups including healthy age matched individuals and patients with peripheral arterial disease[242,258]. Ten out of the 12 studies [256] reported fibrinogen concentrations in men and women combined, while one study reported them separately [256] and another study only reported on men[245].

Nine studies revealed a significantly higher level of plasma fibrinogen in patients with AAA with three studies showing no significant difference. Pooled analysis of the data (Figure 5.2) shows patients with AAA have a significantly higher plasma concentration of fibrinogen, mean difference (MD) 0.43g/l [95% confidence interval 0.28g/l to 0.58g/l] P = <0.00001. There was significant heterogeneity between studies (I^2 = 83%) and accordingly a random effects model was used. Sensitivity analysis was performed and did not significantly change the overall effect. A positive association between AAA size and plasma fibrinogen [245] has been suggested, however meta-regression of studies[245,247,250,251,253] reporting AAA diameter and fibrinogen concentration did not reveal a significant association.

Figure 5.2, Forest plot comparing mean plasma concentration of fibrinogen between studies. A random effects model was used for meta-analysis



D-Dimer

Eleven studies reported on concentrations of plasma D-Dimer[243,244,248-253,259-261] the largest of which contained 1,260 [248] patients while the smallest contained twenty eight[261]. Recruitment was similar between studies, all recruiting from a hospital based setting except one which also recruited from a population setting [248]. Methods varied between studies although in general USS detected AAA patients were compared against aged matched healthy controls. One study compared ultrasound detected small aneurysms (>3cm and <5.5cm) to aged matched controls [253], another compared ultrasound or CT detected AAA (>3cm) patients with both symptomatic atherosclerosis patients and aged matched controls [248]. Ten studies found a significantly increased concentration of plasma D-Dimer in patients with AAA while one found no significant difference. Pooled analysis of the data (Figure 5.3) shows patients with AAA have a significantly higher plasma concentration of D-Dimer, MD 325.82ng/ml [95% confidence interval 199.74ng/ml, 451.89ng/ml] p= <0.00001. There was significant heterogeneity between studies (I^2 = 80%) and accordingly a random effects model was used. Five studies reported on the association of AAA size with plasma concentration of D-Dimer [243,244,247-249] all finding a positive association with the largest correlation coefficient value equalling 0.644[243]. Meta-regression of studies reporting AAA diameter and D-Dimer concentration [244,248,250,251,253,254] (Figure 5.4) reveals a highly significant, strongly positive association between aneurysm diameter and D-Dimer concentration (r^2=0.94 p=<0.0001). Interestingly one study[248] also analyzed the association of D-Dimer with aneurysm growth rate finding a higher concentration of D-Dimer (>900ng/ml) in patients with a growth rate of (1.7mm/year) while patients with a slower growth rate (0.7mm/year) had a significantly lower D-Dimer concentration (≤150ng/ml).

Two studies [243,247] stood as clear outliers within the D-Dimer analysis finding significantly elevated levels of D-Dimer in both the AAA and control group. Unfortunately we were unable to contact the authors to ascertain possible reasons for these differences and closer analysis of the studies does not explain the differences observed. Excluding these studies from the meta-analysis does not change the overall effect MD 290.76ng/ml [95% confidence interval 183.01ng/ml, 398.51ng/ml] P = <0.00001. Sensitivity analysis was performed and the plasma D-Dimer concentration remained significantly elevated in patients with AAA.

Figure 5.3 – Forest plot comparing mean plasma concentration of D-Dimer between studies. A random effects model was used for meta-analysis.

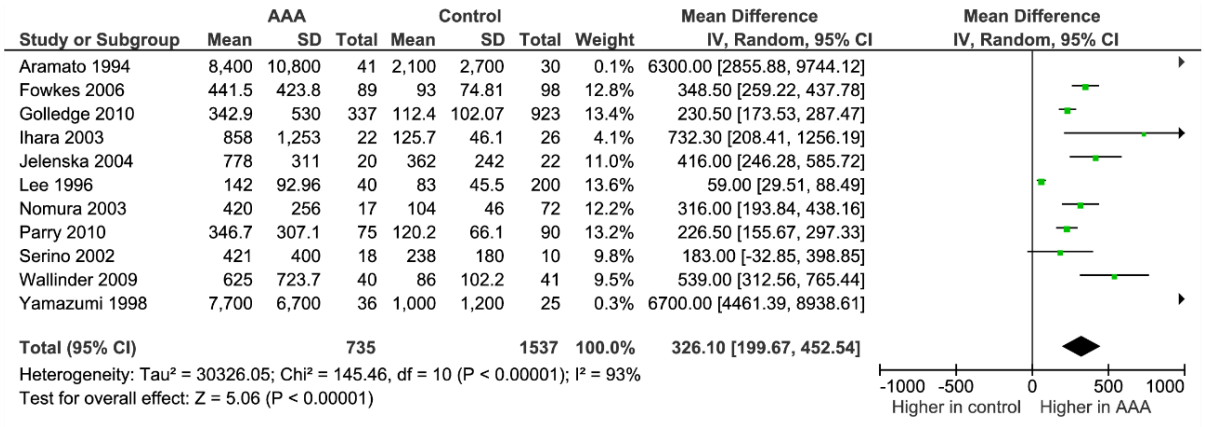
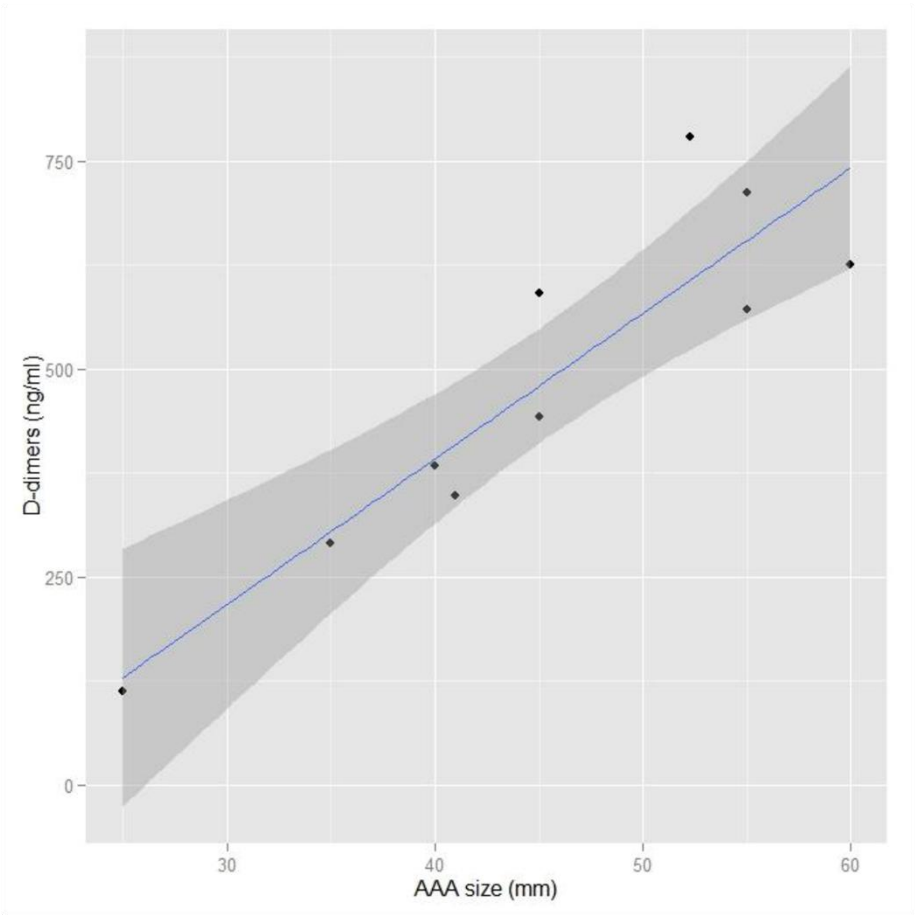


Figure 5.4 – Meta regression demonstrating the association between AAA diameter and D-Dimer concentration.

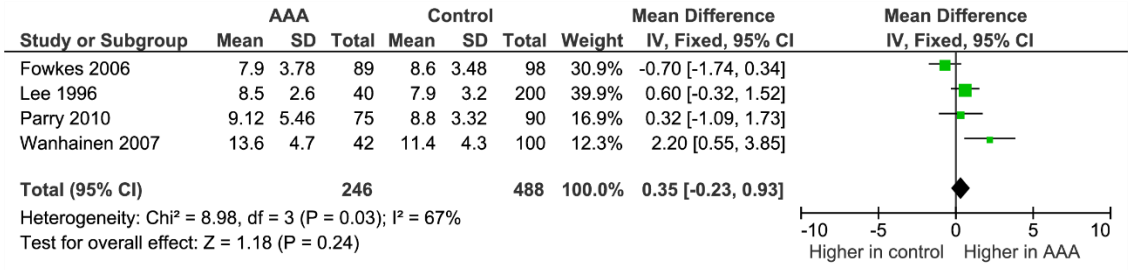


Tissue plasminogen activator (tPA)

Four studies reported concentrations of plasma tPA[250,252,253,262] the largest of which contained 240 patients [252] while the smallest contained 142 patients[262]. Methods were similar between three of the studies in that they compared USS detected AAA to age matched controls however Fowkes et al[250] AAA group had a higher number of smokers and patients with COPD. Three studies reported no significant difference between plasma concentrations of tPA in patients with and without AAA while one study found patients with AAA have a significantly higher concentration of tPA. Pooled analysis of the data (Figure 5.5) reveals patients with AAA do not have a significantly different plasma concentration of tPA

to patients without, MD 0.35ng/ml [95% confidence interval -0.23 ng/ml, 0.93 ng/ml] P = 0.24. There was no significant heterogeneity between studies (I^2 = 43%) and accordingly a fixed effect model was used. Sensitivity analysis was not possible due to included study sizes.

Figure 5.5 – Forest plot comparing mean plasma concentration of tissue plasminogen activator between studies. A fixed effects model was used for meta-analysis.



Plasminogen activator inhibitor type 1 (PAI-1)

Two studies analysed the concentration of PAI-1[244,253] in patients with and without AAA neither of which found a significant difference between the two groups. One study analysed PAI-1 activity [257] again finding no significant difference between patients with AAA and aged matched controls.

Plasmin antiplasmin complexes (PAP)

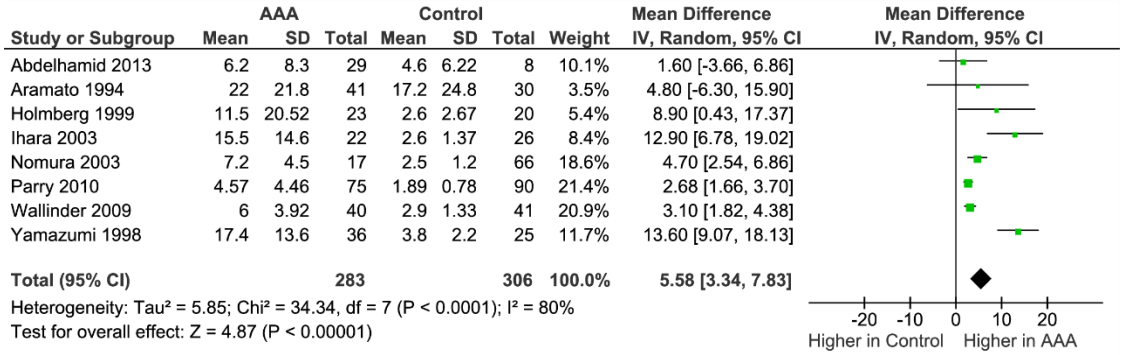
One study [263] reported that PAP is significantly, positively correlated with AAA progression (r = 0.39; [95% confidence Interval, 0.16-0.56] P = < 0.001), a finding which persisted even after adjustment for initial AAA size and smoking. Interestingly they also found that PAP levels were significantly predictive for which cases would reach 55mm within 5 years.

Thrombin-antithrombin III-complex (TAT)

Eight studies reported concentrations of TAT[243,244,249,253,254,259,260,257] the largest of which contained 165[253] patients while the smallest contained 43 patients[254]. Two studies found no significant difference in patients with and without AAA while 6 studies found a significantly higher TAT concentration in patients with AAA. Pooled analysis of the data (Figure 5.6) reveals patients with AAA have a significantly higher plasma concentration of TAT, MD 5.58 g/l [95% confidence interval 3.34 g/l, 7.83 g/l] P = <0.0001. There was significant heterogeneity between studies (I^2 = 80%) and accordingly a random effects model was used. Sensitivity analysis was performed and did not significantly change the overall effect.

Three studies reported on the association of AAA size with plasma concentration of TAT [243,244,249] each finding a positive association with the largest correlation coefficient value equaling 0.714[249]. However, Meta regression of studies[243,244,253,254,257] reporting AAA diameter and TAT concentration revealed no significant association (p=0.5).

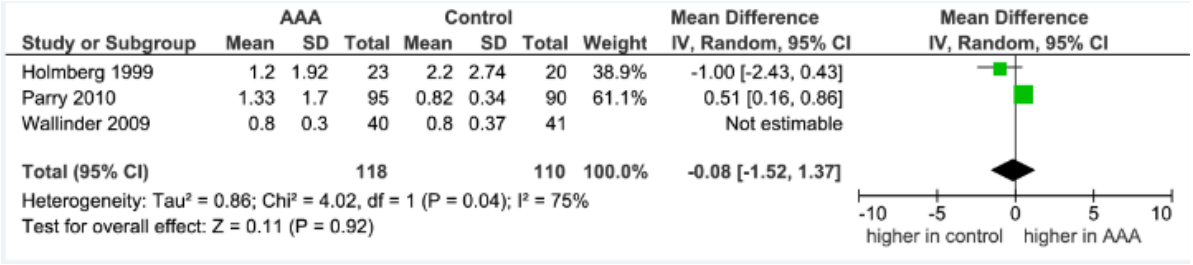
Figure 5.6 – Forest plot comparing mean plasma concentration of Thrombin-antithrombin III-complex between studies. A random effects model was used for meta-analysis.



Prothrombin fragments F1+F2 (F1+2)

Three studies analysed the concentration of F1+2 ([244,253,254]) from which two studies found a significant elevation in patients with AAA while one found no difference. Pooled analysis of the data (Figure 5.7) reveals patients with AAA do not have a significantly different plasma concentration of F1+2 MD 0.11ng/ml [95% confidence interval -0.39 ng/ml, 0.61 ng/ml] p= 0.66. There was significant heterogeneity between studies (I^2 = 75%) and accordingly a random effects model was used. Sensitivity analysis was not possible due to included study sizes.

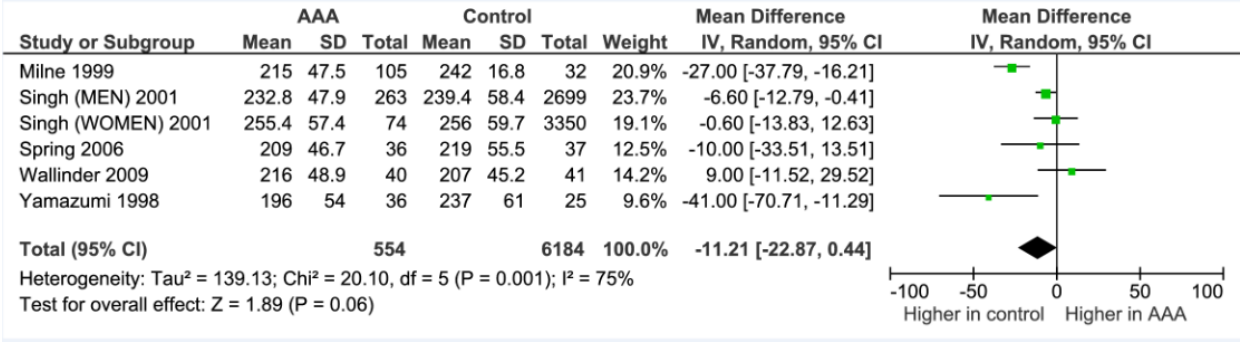
Figure 5.7- Forest plot comparing mean plasma concentration of prothrombin fragments F1+F2 between studies. A random effects model was used for meta-analysis.



Platelet count

Six studies reported differences in platelet count [241,243,244,256,264] the largest of which contained 3,424 patients[256] whilst the smallest had sixty one[243]. Individually two of the studies found a significantly lower platelet count in patients with AAA whilst four did not find any difference. Pooled analysis of the data (Figure 5.8) reveals patients with AAA and controls do not have a significantly different platelet count, MD -11.21x10^{-9} [95% confidence interval -22.87x10^{-9}, 1.54 x10^{-9}] P = 0.06). There was significant heterogeneity between studies (I^2 = 75%) and accordingly a random effects model was used. Sensitivity analysis was performed and did not significantly change the overall effect.

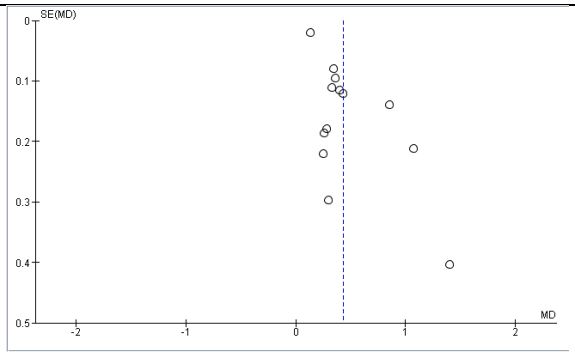
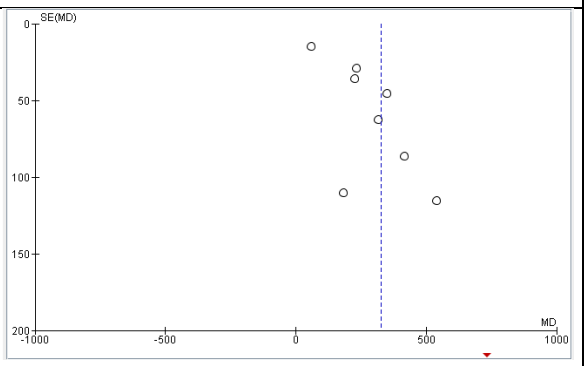
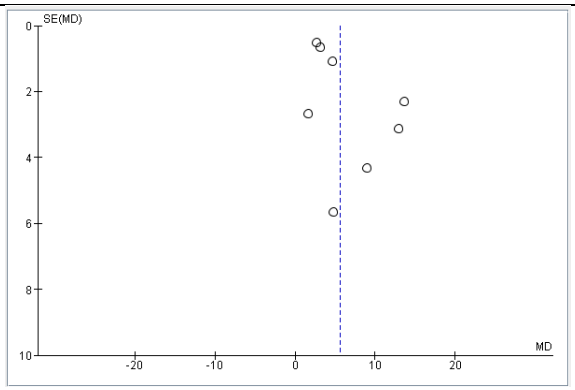
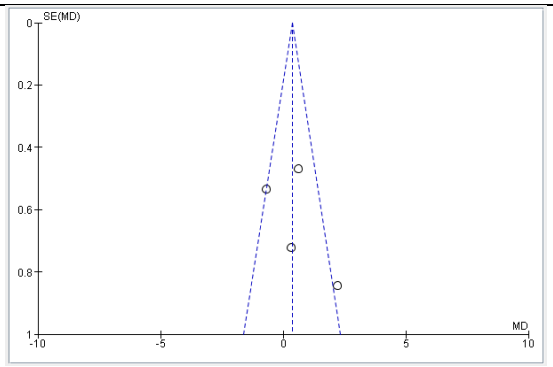
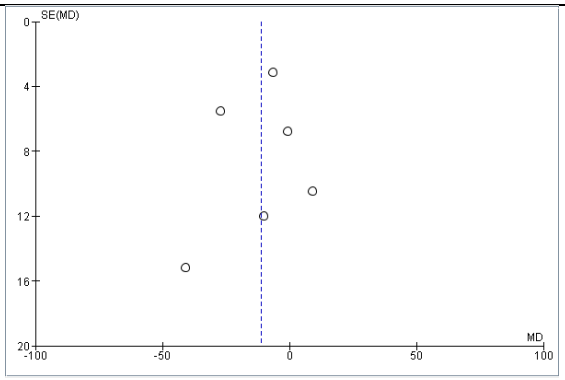
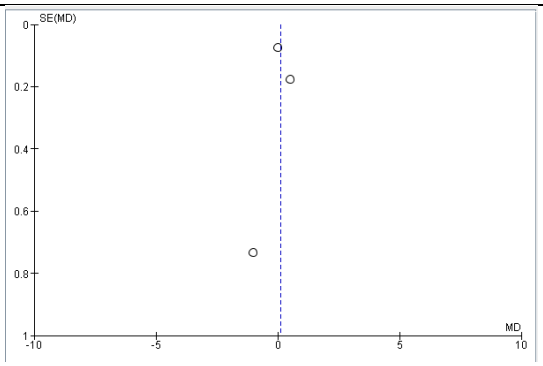
Figure 5.8 – Forest plot comparing mean plasma concentration of platelet count between studies. A random effects model was used for meta-analysis.



Sensitivity analysis and publication bias

Sensitivity analysis through sequential exclusion of individual studies did not significantly alter results for any biomarkers (results not included). Funnel plots did not identify any publication bias (Figure 5.9).

Figure 5.9 Funnel Plots for meta-analyses

Fibrinogen	D-Dimer
	
TAT	**tPA**
	
Platelet count	**F1 +2**
	

Discussion

This systematic review and meta-analysis comparing haemostatic markers in patients with and without AAA represents one of the largest of its kind to date and reveals that there is a significant association between the presence of AAA and plasma levels of fibrinogen, D-Dimer and TAT suggesting that AAA is associated with increased fibrin turnover, fibrinolysis and thrombin generation. Apart from its possible usefulness as a marker of aneurysm presence, a significant linear association exists between D-Dimer concentration and aneurysm diameter suggesting it may also be useful as a marker of endoleak and sac expansion in patients with type II endoleak.

The findings of this study are in keeping with a previous meta-analysis by Takagi et al[236] who demonstrated a significantly higher fibrinogen and D-Dimer concentration in patients with AAA compared to a control group. By the inclusion of the most recent studies analysing fibrinogen and D-Dimer we have been able to refine the results previously published to MD 0.43g/l [95% confidence interval 0.28 g/l, 0.58 g/l] P = <0.00001) and MD 325.82ng/ml [95% confidence interval 199.74 ng/ml, 451.89 ng/ml] P = <0.00001) respectively. Several studies have reported elevated levels of haemostatic markers in patients with atherosclerosis, therefore by excluding patients with peripheral vascular disease from the control groups which has not been done previously; these results should better reflect true differences between patients with AAA and normal healthy individuals.

The finding of an association between plasma fibrinogen, D-Dimer and TAT concentration and the presence of AAA is important in that it reflects the pathophysiology of AAA. The coagulation cascade involves a complex series of enzymatic reactions that culminate in thrombin generation and the deposition of insoluble fibrin. TAT is an established marker of

thrombin activation, whereas the action of plasmin on cross-linked fibrin generates degradation products including D-dimer[253].Whilst it is possible that markers of haemostasis are involved in the development of AAA as D-Dimer has itself been shown to stimulate the release of pro-inflammatory cytokines and proteolytic enzymes[265], plasma markers of coagulation are known to fall following aortic aneurysm repair (although not necessarily to that seen in patients without AAA)[266] suggesting that the aneurysm itself drives the changes observed in this study, reflecting the size and continual remodelling of the intraluminal thrombus[243]. This progressive coagulopathy appears to be proportional to aortic diameter and given that a link between markers of haemostasis and atherothrombosis is both likely and plausible, this highlights the importance of addressing all modifiable cardiovascular risk factors in patients with AAA.

Elevated levels of haemostatic markers have been reported in patients with atherosclerosis, smokers and as an acute phase response for example in patients with infections however the majority of studies in this review did not control for these variables. Golledge et al[248] showed that D-Dimer levels are higher in AAA patients as compared with those with peripheral artery disease alone. Five studies [248,253,256,262,267] had a significantly higher number of smokers in their AAA group however Lee et al[252] showed that after adjustments for pack years, a SD increase (0.76 g l^{-1}) in fibrinogen was associated with a significant increase in the risk of AAA. One study[243] excluded patients with a C-reactive protein >0.4mg/dl in an attempt to exclude patients whose markers may be raised as an acute phase response finding significantly elevated levels of TAT and D dimer with a significantly lower platelet count.

One limitation of this study is that some of the included studies have small patient numbers and the number of patients in the meta-analysis of TAT is significantly smaller than that for fibrinogen or D-Dimer however, inclusive of all studies we were able to analyse 9,862 patients. Another limitation is that it does not take into account that some patients with AAA have little or no mural thrombus and most of the studies included did not quantify levels of thrombus based on radiographic data. Yamazumi and colleagues[18] demonstrated that maximum thickness of mural thrombus is significantly, positively correlated with preoperative levels of TAT and D-Dimer with another study[20] finding fibrinogen levels to be positively correlated with the percentage of intraluminal thrombus occupying the lumen ($r = 0.36$; $P<0.05$). Shindo et al[22] however revealed that while thrombus volume was strongly correlated with the volume and diameter of the AAA ($r = 0.6$ $P = <0.01$), it was not associated with coagulation factors. Taken together these findings suggest these markers may not be useful in patients with little or no intra-luminal thrombus. Future studies of the use of haemostatic markers in identifying patients with AAA should match patients for both age and smoking habits and should exclude patients with peripheral vascular disease. An ideal method of reporting biomarker studies would be using ROC curves however only Golledge *et al*[248] reported an AUC of 0.83 for D-Dimer.

Summary

1. **D-Dimer is significantly associated with AAA presence and diameter**
2. **Fibrinogen and TAT are significantly associated with AAA presence**
3. **D-Dimer may be a suitable marker of type II endoleak presence and sac expansion**

5.2 Study of biomarkers of type II endoleak

I have presented evidence in the previous section that D-Dimer appears to be found in higher concentrations in patients with AAA (compared to those without) and that the D-Dimer concentration appears to increase as the aneurysm sac increases. Plasma markers of coagulation such as D-Dimer are known to fall following aortic aneurysm repair[266] and previous studies have also demonstrated that D-Dimer may be a useful marker of incomplete aneurysm exclusion after EVAR[231]. These findings are likely to reflect the removal of the aortic thrombus present in the majority of AAA's from the circulation therefore my hypothesis within this section is that as the presence of a type II endoleak allows a persistent and direct communication between the aortic thrombus and arterial blood flow (via outflow vessels) that it is plausible that the presence of a type II endoleak and continued sac expansion may be measurable peripherally by utilising markers of coagulation.

I have included three markers of coagulation to assess their usefulness as a biomarker of type II endoleak presence and sac diameter. D-Dimer is a fibrin degradation product, thus reflects the extent of fibrin turnover in the circulation and is included as it has repeatedly been associated with the presence and size of AAA[268,269] as described earlier. Fibrinogen is synthesised in the parenchymal cell of the hepatocyte and plays a major role in the coagulation pathway in that it is cleaved by thrombin in the final stages to produce fibrin that self assembles to form an insoluble fibrin clot by cross-linking with factor XIIIa. Those with elevated Fibrinogen levels appear to have a higher risk of AAA, which may correlate with the amount of parietal thrombus[236,270] and although I was unable to demonstrate an association between Fibrinogen and AAA diameter, it may be a useful marker of type II endoleak.

Lastly, Kininogen is produced by the liver and is a cofactor for the activation of prekallikrein, Factor XII, and Factor XI. Kininogen has been demonstrated to be up-regulated in those patients with AAA (p=0.003, AUC=0·86)[271] and has previously been investigated within the department. The aim of this study was to investigate the above coagulation factors as potential biomarkers of type II endoleak presence and aneurysm sac size.

Methods

Ethical approval was obtained (REC: 6819; An investigation into candidate genes and protein profiling for abdominal aortic aneurysms. Chief Investigator Professor Robert Sayers, University of Leicester) permitting the collection of blood from patients with AAA. Consent was obtained for all subjects prior to inclusion within the study. In order to assess the value of markers of coagulation to detecting endoleak patients were only included if they were to undergo EVAR at a single centre. Patients who were planned for OSR were excluded.

40 matched pre-operative and post-operative EVAR patients were included in addition to 30 patients identified as having a type II endoleak post EVAR. Peripheral blood samples were taken at rest, pre-operatively and at least 6 weeks post operatively. Plasma samples were obtained by taking whole blood directly into EDTA tubes. These tubes were kept at room temperature and processed immediately. The samples were spun at 2,000g (unrefrigerated centrifuge) for 10 minutes. The plasma was then collected in 600ul aliquots into 1.5ml processing tubes. These were then spun at 10,000g for 10 minutes to remove the platelets. Plasma was then pipetted off taking care to avoid the platelet pellet, and stored at -80°C. Plasma samples remained frozen until thawed prior to ELISA's being performed. ELISA's were performed by myself using standard commercial assays designed to detect Human Fibrinogen (Abcam ab108842 protocol), Kininogen (Abcam ab108875

protocol) and D-Dimer (Hyphen Biomed ARK023A protocol). The protocols used for this study can be found in appendix 2. Each sample was analysed in triplicate with the mean of the triplicate utilised as discussed in the triplicate section.

Patients included were entered onto a prospective database. DUSS was performed using a GE Logiq E9 scanner (Fairfield, USA) with a C1-5 MHz broadband curved array transducer (B-mode imaging, colour flow imaging and spectral Doppler modalities). Type II endoleak was defined as retrograde blood flow outside of the endograft but within the aneurysm sac from aortic side branches. Pre-operative and post-operative data regarding sac size (outer wall to outer wall) was measured in both antero-posterior and lateral planes and the presence or absence of endoleak was recorded.

Statistics

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) depending on the variance. Analysis of Variance (ANOVA) was performed to look for differences between the means of three groups namely, pre-operative, post-operative and type II endoleak. Where a significant difference in the mean between groups was identified, T-test was used to look for differences between two groups namely pre-operative *versus* post-operative and post-operative *versus* type II endoleak. Where differences were seen between post EVAR marker concentrations and those with type II endoleak, these concentrations were plotted against aneurysm sac diameter and standard linear regression performed to look for any association between marker concentration and aneurysm diameter. All statistical analyses were performed using SPSS v.20 (IBM Corp, Armonk, NY) and assumed to be significant if P equalled less than 0.05.

Results

A total of 70 patients were included into the study (Table 5.1). From this 40 patients donated matched pre-operative and post-operative blood samples however only four of these patients had developed a type II endoleak by the end of the study period. The prevalence of type II endoleak within this cohort of patients was in fact much lower than that anticipated at the beginning of the study (a prevalence as high as 44% has been reported) and this reflects a number of important findings noted in earlier sections of the thesis. Firstly, the earlier literature review of type II endoleaks demonstrated that only 10% of patients post EVAR develop a type II endoleak. Secondly, the review of data from the Leicester Royal Infirmary suggested that of all of the type II endoleaks that do occur over a mean follow up of 3.6 years (much longer then I was able to achieve in this study), a significant number occur

late (more than one year post EVAR. Due to this unexpectedly low number of type II endoleaks within the matched group I did not perform an analysis of matched pre and post op type II endoleaks. I instead performed an analysis of unmatched pre-operative samples with post-operative samples from patients with type II endoleaks.

ANOVA (Table 5.2) suggests that whilst Fibrinogen (Figure 5.10, P = 0.311) demonstrates no differences between the groups, significant differences were seen for Kininogen (Figure 5.11, P = 0.0001) and D-Dimer (Figure 5.12, P = 0.0001). As such Kininogen and D-Dimer were compared for differences between pre-operative *versus* post-operative and post-operative *versus* type II endoleak. Kininogen demonstrates a difference between the pre-operative and post-operative groups (P = 0.0001) however no differences were seen between the post-operative group and those with type II endoleak (P = 0.076). D-Dimer demonstrated no significant difference between the pre and post EVAR groups (P = 0.145), however, differences were seen between those post EVAR and those with type II endoleak (P = 0.0001). Although D-dimer appears to be significantly higher in those patients with type II endoleak, we were unable to demonstrate and linear relationship between D-Dimer concentration and sac diameter (figure 5.13).

Table 5.1 – Demographics of patients included into the study

	Matched Samples ***n* = 40**	**Type II Endoleak** **N=30**
Age (SD)	73.5 (12.6)	74 (10.1)
Male (%)	35 (87.5)	27 (90)
Aneurysm Diameter (SD)	62.2 (8.8)	65.0 (13.5)

Table 5.2 – Descriptives of assays performed within this study including both intra and inter coefficients of Variation.

	Fibrinogen μg/ml Mean (SD)	Kininogen μg/ml Mean (SD)	D-Dimer ng/ml Mean (SD)
Pre-operative	6.8 (6.1)	-2.1 (1.7)	40.7 (38.7)
Post-Operative	8.9 (7.6)	0.35 (0.8)	52.8 (34.4)
Type II Endoleak	9.2 (9.1)	0.7 (1.0)	138.4 (44.0)
Intra-assay %CV	4.9	4.9	5.0
Inter – assay % CV	7.3	7.1	8.0

CV = Coefficient of Variation

Figure 5.10 – Box and Whisker plot demonstrating no difference in Fibrinogen concentration between those with and without type II endoleak post EVAR (P = 0.311).

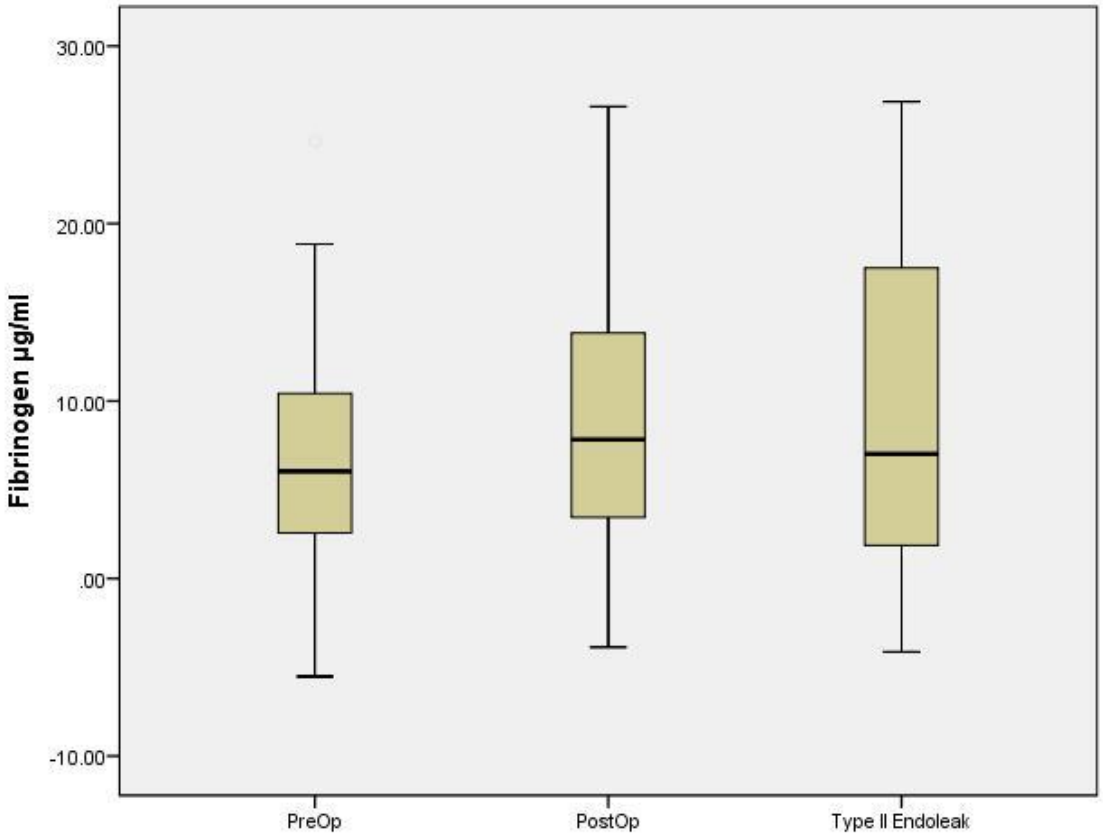


Figure 5.11 – Box and Whisker plot demonstrating no difference in Kininogen concentration between those with and without type II endoleak post EVAR (P = 0.076).

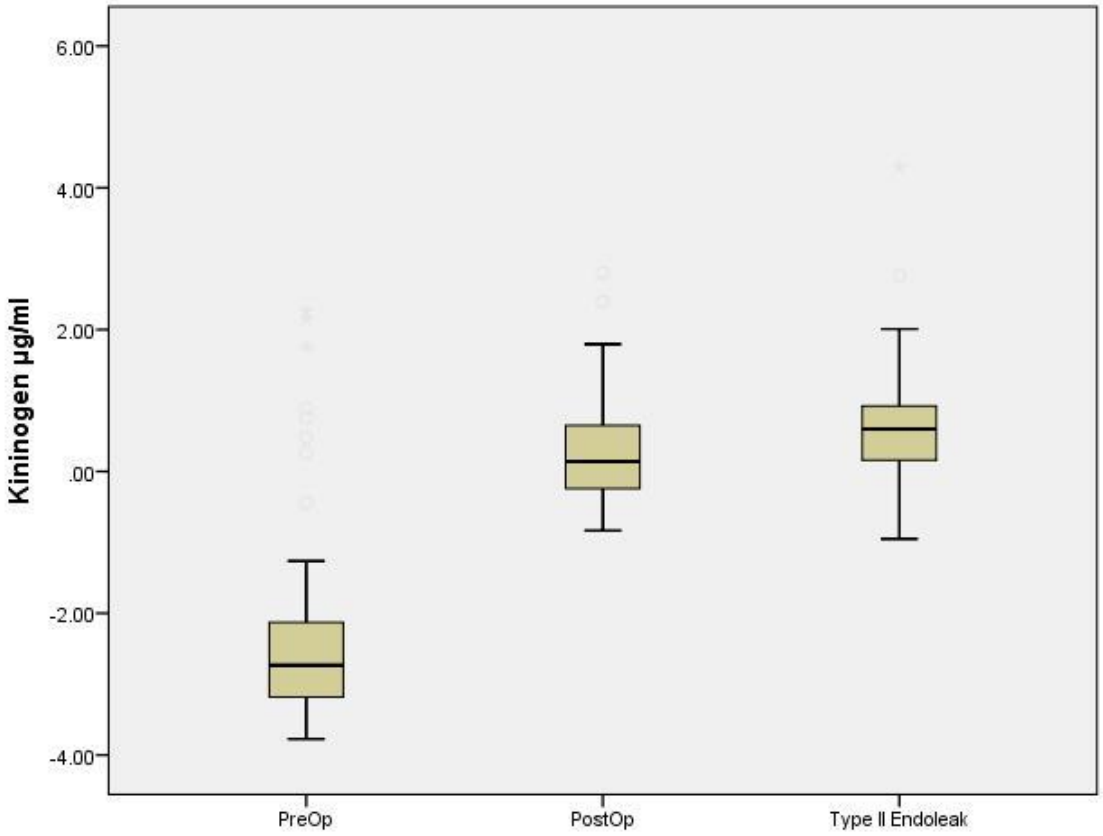


Figure 5.12 – Box and Whisker plot demonstrating a significant difference in D-Dimer concentration between those with and without type II endoleak post EVAR (P = 0.0001).

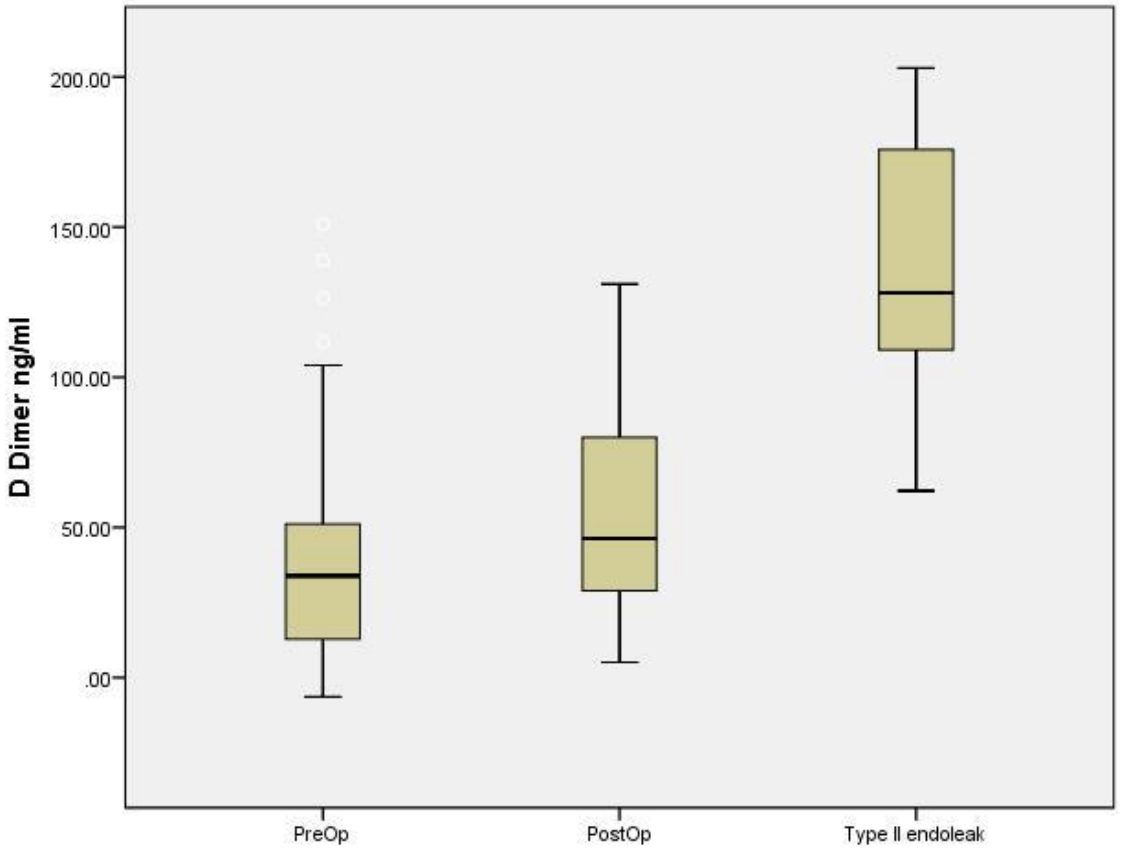
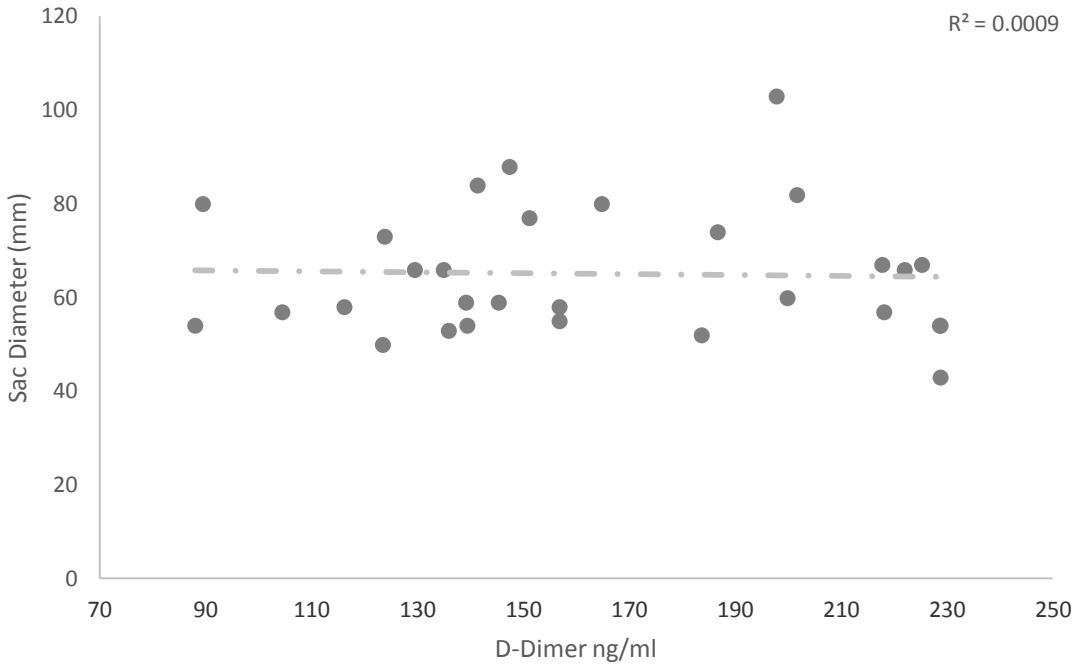


Figure 5.13 – Linear Regression suggesting no association between D-dimer concentration and sac size post EVAR (Type II Endoleak group)



Conclusions

This study analysed potential markers of type II endoleak post EVAR, finding that those with type II endoleak appear to have a significantly higher D-Dimer concentration then their contemporaries without type II endoleak. This study also suggests that Kininogen which acts a co-factor for coagulation, increases post-operatively which is perhaps unsurprising, however, is not increased in those with type II endoleak. Fibrinogen concentrations were not significantly different in those with type II endoleak compared to those without.

A biomarker of type II endoleak would be clinically useful in that a cheap, sensitive test to highlight those patients at risk of complication and requiring a more expensive test, for example duplex ultrasound, could save money. Currently we have been able to demonstrate

that the D-Dimer concentration is higher in those patients with a type II endoleak compared to those without, however, D-Dimer is a notoriously non-specific marker known to be raised in a number of acute cardiovascular pathologies for example aortic dissection[272], pulmonary embolism[273] and acute mesenteric ischaemia[274] to name a few. Furthermore, that D-dimer is raised in those with type II endoleak does not mean that it would be a sensitive test for type II endoleak and it is likely to be raised in those with other complications of EVAR for example high pressure endoleaks and limb occlusions. At the moment I do not therefore have enough evidence to suggest that D-Dimer would be a sensitive marker of type II endoleak.

This body of work has demonstrated that the mere presence of a type II endoleak is not necessarily important clinically. In fact it is those patients with a type II endoleak and significant sac expansion who appear to be more clinically relevant and this data does not suggest any association between D-Dimer concentration and sac diameter despite the findings of the earlier meta-analysis. Furthermore, this study cannot differentiate between marker concentrations and aneurysm sac growth rates which would be even more useful.

To be useful in the clinical setting, a biomarker of type II endoleak would have to be able to differentiate those with type II endoleak and sac expansion from those without. Modern duplex scanning has a sensitivity and specificity approaching 90%[226] for the detection of endoleaks requiring intervention and can identify sac expansion in addition to a number of other important complications. DUSS therefore currently has a number of important advantages over the markers analysed in this study. One limitation of this study was the low number of patients who developed type II endoleak post EVAR although this is the largest study of biomarkers in patients with type II endoleak to date. Studies have previously shown

a varying prevalence of type II endoleak varying between 10% and 40%[180], however, within the matched cohort of 40 patients, only a few patients developed type II endoleak. With a longer follow up, some of the matched cohort of patients may go on to develop late type II endoleak. Another limitation is that this study utilised aortic sac diameter at the time the blood sample was taken. Ideally, repeated duplexes would be required to identify individual aneurysm growth rates for each patient, which could then be correlated with marker concentrations to look for associations.

Summary

1. **D-Dimer is significantly higher in patients with a type II endoleak**
2. **D-Dimer is not associated with AAA sac diameter**

Overall Conclusions

Within this thesis I have presented the largest population based analysis of AAA mortality to date which confirms that AAA mortality is declining in most developed economies; however that this decline is not equal between countries, gender or age groups. This is the first study to demonstrate a linear relationship between global variations in common cardiovascular risk factors and AAA mortality suggesting that public health measures to reduce the prevalence of hypertension, high cholesterol and smoking could reduce the global burden of AAA further. Using similar methods we have been able to add to growing evidence that the aorta is a heterogeneous structure with varying influences above and below the diaphragm. Smoking is the main modifiable risk factor in the development of AAA but this does not appear to be the case for TAA.

Type II endoleak is the most common complication of EVAR and one of the most common indications for intervention. This is important because a surplus of interventions in patients undergoing EVAR compared to OSR has led to an erosion of many of the benefits seen in patients after EVAR. This body of work has demonstrated that the conservative management of type II endoleak is not associated with an increase in the risk of aneurysm related mortality, all-cause mortality, 10mm of sac expansion or type I endoleak. In the absence of more than 10mm of sac expansion, it appears to be safe to treat type II endoleak conservatively. Furthermore, type II endoleaks appear to have a good chance of spontaneously resolving without any intervention.

Summary

- The largest population based analysis of aneurysm mortality to date.
- Mortality from AAA is not declining globally and is not equal between genders.
- AAA Mortality is associated with several cardiovascular risk factors.
- The decline in mortality appears to be more profound in the under 75 age group.
- Mortality from TAA is generally declining much like seen for AAA.
- No association between changes in smoking prevalence and TAA mortality.
- Public health measures could reduce mortality from AAA.
- Rupture post EVAR secondary to an isolated type II endoleak is rare (0.9%).
- A third of endovascular interventions are not successful at embolising the type II endoleak.
- 10-19% of patients develop type II endoleak post EVAR.
- 32-54% of type II endoleak spontaneously resolve.
- No association with type I endoleak and type II endoleak.
- A conservative approach to type II endoleak appears to be safe in the absence of significant sac expansion and results in no increase in aneurysm related mortality.
- D-Dimer is significantly higher in patients with a type II endoleak however does not appear to be useful as a biomarker.

Further Research

Epidemiology

One of the crucial observations that this thesis highlights is the declining mortality from AAA across many developed countries. Although some have suggested this may represent a reduction in the prevalence of AAA (secondary to cardiovascular risk factor modification), this has not been proven. I plan to analyse the current prevalence of AAA (in both men and women) over time for a number of reasons.

1) If the prevalence of AAA is declining in men this may have implications for the UK aneurysm screening program. Further research utilising current prevalence rates is required to ensure that the screening program remains cost effective. A targeted approach to screening (such as in the United States where only male smokers are screened) may be more cost effective and I plan to investigate its safety, feasibility and cost effectiveness at current AAA prevalence rates.

2) If the prevalence and mortality from AAA is increasing in women, they may fall above the threshold for cost effectiveness. A feasibility study of targeted AAA screening in women utilising primary care databases along with nationally collected patient data (such as that by the office for national statistics, UK) would be useful.

3) The decline in male AAA mortality have led to suggestions that the UK AAA screening program causes excess psychosocial harm for little benefit. Studies utilising AAA specific quality of life instruments/questionnaires to examine the psychological effect of screening at its current prevalence are required to assess this.

4) A patient level analysis of the role of risk factor modification (best medical therapy) in modifying the development of (for example growth rates) and mortality from TAA is required. This will help us better understand differences between AAA and TAA.

5) The observation that obesity demonstrates 'reverse epidemiology' in that it is protective in AAA mortality needs further investigation. Body mass index may be surrogate marker for confounders such as healthcare expenditure and this can be examined utilising ecological regression. Ideally this should be validated within each country by examining geographical districts separately. A study comparing the effect of body mass index *versus* central adiposity would also be useful to define whether general obesity or central adiposity (intra-abdominal fat) is important in the development (or protection) from AAA.

6) 'Public health measures could further reduce mortality from AAA' is one of the main messages from this thesis. The UK AAA Screening program advocates cardiovascular best medical therapy and smoking cessation for all those screened positive for AAA. This provides a unique opportunity to study the effect on mortality (all-cause and aneurysm related) of early risk factor reduction (and complications for example bleeding) in this cohort comparative to those not on best medical therapy (for example in those who are not compliant, or those aneurysms found incidentally).

Type II endoleak

In this thesis type II endoleak have been demonstrated to have a high chance of spontaneously resolving with conservative treatment being safe in the absence of sac expansion up to 5mm. This suggests that patients with persistent type II endoleaks (without

sac expansion) and those with minimal sac expansion do not require intervention. Future research needs to focus on.

1) The risk of type II endoleak with aneurysm sac expansion in excess of 5mm. A randomised controlled trial comparing conservative *versus* selective *versus* aggressive treatment in those group is unlikely therefore a multicentre registry may be the best way forward to collect and examine this. Medium and Long term data are required.

2) The role of intervention in those with type II endoleak remains unclear. A randomised controlled trial comparing approaches (transarterial *versus* translumber) and different embolents is required to find a 'gold standard' pathway. Similar to above, this may be easier achieved through the formation of an international, multicentre type II endoleak registry.

3) Further research could also include a study of the association between aneurysm sac size changes in patients with type II endoleak, and changes in the aneurysm neck. This may help us understand why some patients with type II endoleak and sac expansion get complications (such as rupture), while others do not.

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Appendix 2 – ELISA Protocols

Fibrinogen

Abcam, Ab108842

1 REAGENT PREPARATION

Equilibrate all reagents to room temperature (18-25°C) prior to use. Prepare fresh reagents immediately prior to use. If crystals have formed in the concentrate, mix gently until the crystals have completely dissolved.

1.1 1X Diluent N

Dilute the 10X Diluent N Concentrate 1:10 with reagent grade water. Mix gently and thoroughly. Store for up to 1 month at 4°C.

1.2 1X Wash Buffer

Dilute the 20X Wash Buffer Concentrate 1:20 with reagent grade water. Mix gently and thoroughly.

1.3 1X Biotinylated Fibrinogen

Add 4 mL 1X Diluent N to the lyophilized Biotinylated Fibrinogen vial to generate a 2X Biotinylated Fibrinogen stock solution. Allow the vial of 2X Biotinylated Fibrinogen stock solution to sit for 10 minutes with gentle agitation prior to use. The stock solution should be further diluted 1:2 with 1X Diluent N to generate the 1X Biotinylated Fibrinogen.

Any remaining solution should be frozen at -20°C.

1.4 1X SP Conjugate

Spin down the 100X Streptavidin-Peroxidase Conjugate (SP Conjugate) briefly and dilute the desired amount of the conjugate 1:100 with 1X Diluent N.

Any remaining solution should be frozen at -20°C.

STANDARD PREPARATIONS

- Prepare serially diluted standards immediately prior to use. Always prepare a fresh set of standards for every use.
- Any remaining standard should be stored at -20°C after reconstitution and used within 30 days.
- This procedure prepares sufficient standard dilutions for duplicate wells.

2 Reconstitution of the Fibrinogen Standard vial to prepare the 40 µg/mL Fibrinogen Standard #1.

2.1 First consult the Fibrinogen Standard vial to determine the mass of protein in the vial.

2.2 Calculate the appropriate volume of 1X Diluent N to add when resuspending the Fibrinogen Standard vial to produce the 40 µg/mL Standard #1 by using the following equation:

CS = Starting mass of Fibrinogen Standard (see vial label) (µg)

CF = The 40 µg/mL Fibrinogen Standard #1 final required concentration

VD = Required volume of 1X Diluent N for reconstitution (µL)

Calculate total required volume 1X Diluent N for resuspension:

(CS /CF) X 1,000 = VD Example:

NOTE: This example is for demonstration purposes only. Please remember to check your standard vial for the actual amount of standard provided.

CS = 100 µg of Fibrinogen Standard in vial

CF = 40 µg/mL Fibrinogen Standard #1 final concentration VD = Required volume of 1X Diluent N for reconstitution

(100 µg / 40 µg/mL) X 1,000 = 2,500 µL

2.3 First briefly spin the Fibrinogen Standard vial to collect the contents on the bottom of the tube.

2.4 Reconstitute the Fibrinogen Standard vial by adding the appropriate calculated amount VD of 1X Diluent N to the vial to generate the 40 µg/mL Standard #1. Mix gently and thoroughly.

2.5 Allow the reconstituted 40 µg/mL Standard #1 to sit for 10 minutes with gentle agitation prior to making subsequent dilutions

2.6 Label six tubes #2 – 7.

2.7 Add 240 µL of 1X Diluent N to tube #2 – 7.

2.8 To prepare Standard #2, add 120 µL of the Standard #1 into tube #2 and mix gently.

2.9 To prepare Standard #3, add 120 µL of the Standard #2 into tube #3 and mix gently.

2.10 Using the table below as a guide, prepare subsequent serial dilutions.

2.11 1X Diluent N serves as the zero standard, 0 µg/mL (tube #7).

Standard Dilution Preparation Table

Standard #	Volume to Dilute (µL)	Volume Diluent N (µL)	Total Volume (µL)	Starting Conc. (µg/mL)	Final Conc. (µg/mL)
1	**Step 10.1**				**40.00**
2	**120**	**240**	**360**	**40.00**	**13.33**
3	**120**	**240**	**360**	**13.33**	**4.444**
4	**120**	**240**	**360**	**4.444**	**1.481**

5	**120**	**240**	**360**	**1.481**	**0.494**
6	**120**	**240**	**360**	**0.494**	**0.165**
7	**-**	**240**	**240**	**-**	**0**

3 SAMPLE PREPARATION

3.1 Plasma

Collect plasma using one-tenth volume of 0.1 M sodium citrate as an anticoagulant. Centrifuge samples at 2,000 x g for 10 minutes and use supernatants for assay. Dilute samples 1: 2,000 into 1X Diluent N. The undiluted samples can be stored at -20°C or below for up to 3 months. Avoid repeated freeze-thaw cycles (EDTA can also be used as anticoagulant).

4. PLATE PREPARATION

- The 96 well plate strips included with this kit are supplied ready to use. It is not necessary to rinse the plate prior to adding reagents.
- Unused well plate strips should be returned to the plate packet and stored at 4°C.
- For statistical reasons, we recommend each sample should be assayed with a minimum of two replicates (duplicates).
- Well effects have not been observed with this assay. Contents of each well can be recorded on the template sheet included in the Resources section.

5 ASSAY PROCEDURE

- Equilibrate all materials and prepared reagents to room temperature (18-25°C) prior to use.
- It is recommended to assay all standards, controls and samples in duplicate.

5.1 Prepare all reagents, working standards and samples as instructed. Equilibrate reagents to room temperature before use. The assay is performed at room temperature

(18-25°C).

5.2 Remove excess microplate strips from the plate frame and return them immediately to the foil pouch with desiccant inside. Reseal the pouch securely to minimize exposure to water vapor and store in a vacuum desiccator.

5.3 Add 25 µL of Fibrinogen Standard or sample per well and immediately add 25 µL of 1X Biotinylated Fibrinogen to each well (on top of standard or sample). Cover wells with a sealing tape and incubate for two hours. Start the timer after the last sample addition.

5.4 Wash five times with 200 µL of 1X Wash Buffer manually. Invert the plate each time and decant the contents; tap it 4-5 times on absorbent paper towel to completely remove the liquid. If using a machine wash six times with 300 µL of 1X Wash Buffer and then invert the plate, decant the contents; tap it 4-5 times on absorbent paper towel to completely remove the liquid.

5.5 Add 50 µL of 1X SP Conjugate to each well and incubate for 30 minutes. Turn on the microplate reader and set up the program in advance.

5.6 Wash microplate as described above.

5.7 Add 50 µL of Chromogen Substrate per well and incubate for about 8 minutes or till the optimal blue colour density develops. Gently tap plate to ensure thorough mixing and break the bubbles in the well with pipette tip.

5.8 Add 50 µL of Stop Solution to each well. The color will change from blue to yellow.

5.9 Read the absorbance on a microplate reader at a wavelength of 450 nm immediately. If wavelength correction is available, subtract readings at 570 nm from those at 450 nm to correct optical imperfections. Otherwise, read the plate at 450 nm only. Please note that some unstable

black particles may be generated at high concentration points after stopping the reaction for about 10 minutes, which will reduce the readings.

Kininogen

1 REAGENT PREPARATION (Abcam, ab108875)

Equilibrate all reagents to room temperature (18-25°C) prior to use. Prepare fresh reagents immediately prior to use. If crystals have formed in the concentrate, mix gently until the crystals have completely dissolved.

1.1 1X Diluent N

Dilute the 10X Diluent N Concentrate 1:10 with reagent grade water. Mix gently and thoroughly. Store for up to 1 month at 4°C.

1.2 1X Wash Buffer

Dilute the 20X Wash Buffer Concentrate 1:20 with reagent grade water. Mix gently and thoroughly.

1.3 1X Biotinylated Kininogen

1.4 The stock Biotinylated Kininogen Antibody must be diluted with 1X Diluent N according to the label concentration to prepare 1X Biotinylated Kininogen Antibody for use in the assay procedure. Observe the label for the "X" concentration on the vial of Biotinylated Kininogen.

1.5 Calculate the necessary amount of 1X Diluent N to dilute the Biotinylated Kininogen Antibody to prepare a 1X Biotinylated Kininogen Antibody solution for use in the assay procedure according to how many wells you wish to use and the following calculation:

Number of Wells Strips	Number of Wells	(V_T) Total Volume of 1X Biotinylated Detector Antibody (µL)
4	**32**	**1,760**

6	**48**	**2,640**
8	**64**	**3,520**
10	**80**	**4,400**
12	**96**	**5,280**

Any remaining solution should be frozen at -20°C.

Where:

CS = Starting concentration (X) of stock Biotinylated Kininogen Antibody (variable)

CF = Final concentration (always = 1X) of Kininogen Antibody solution for the assay procedure

VT = Total required volume of 1X Kininogen Antibody solution for the assay procedure

VA = Total volume of (X) stock Kininogen Antibody

VD = Total volume of 1X Diluent N required to dilute (X) stock Biotinylated Kininogen Antibody to prepare 1X Biotinylated Antibody solution for assay procedures

Calculate the volume of (X) stock Biotinylated Antibody required for the given number of desired wells:

(CF / CS) x VT = VA

Calculate the final volume of 1X Diluent N required to prepare the 1X Biotinylated Von Willebrand Factor Antibody:

VT - VA = VD

Example:

NOTE: This example is for demonstration purposes only. Please remember to check your antibody vial for the actual concentration of antibody provided.

CS = 50X Biotinylated Von Willebrand Factor Antibody stock

CF = 1X Biotinylated Von Willebrand Factor Antibody solution for use in the assay procedure

VT = 3,520 µL (8 well strips or 64 wells)

(1X/50X) x 3,520 µL = 70.4 µL

3,520 µL - 70.4 µL = 3,449.6 µL

VA = 70.4 µL total volume of (X) stock Biotinylated Kininogen Antibody required

VD = 3,449.6 µL total volume of 1X Diluent N required to dilute the 50X stock Biotinylated Antibody to prepare 1X Biotinylated Kininogen

Antibody solution for assay procedures

1.6 First spin the Biotinylated Kininogen Antibody vial to collect the contents at the bottom.

1.7 Add calculated amount VA of stock Biotinylated Kininogen Antibody to the calculated amount VD of 1X Assay Diluent N. Mix gently and thoroughly.

9.4 1X SP Conjugate

Spin down the 100X Streptavidin-Peroxidase Conjugate (SP Conjugate) briefly and dilute the desired amount of the conjugate 1:100 with 1X Diluent N.

Any remaining solution should be frozen at -20°C.

2 STANDARD PREPARATIONS

- Prepare serially diluted standards immediately prior to use. Always prepare a fresh set of standards for every use.

- Any remaining standard should be stored at -20°C after reconstitution and used within 30 days.

- This procedure prepares sufficient standard dilutions for duplicate wells.

2.1 Reconstitution of the Kininogen Standard vial to prepare a 4 µg/mL Kininogen Standard #1.

2.2 First consult the Kininogen Standard vial to determine the mass of protein in the vial.

2.3 Calculate the appropriate volume of 1X Diluent N to add when resuspending the Kininogen Standard vial to produce a 4 µg/mL Kininogen Standard #1 by using the following equation:

CS = Starting mass of Kininogen Standard (see vial label) (µg)

CF = 4 µg/mL Kininogen Standard #1 final required concentration

VD = Required volume of 1X Diluent N for reconstitution (µL)

Calculate total required volume 1X Diluent N for resuspension:

(CS/ CF) x 1,000 = VD

Example:

NOTE: This example is for demonstration purposes only. Please remember to check your standard vial for the actual amount of standard provided.

CS = 6 µg of Kininogen Standard in vial

CF = 4 µg/mL Kininogen Standard #1 final concentration VD = Required volume of 1X Diluent N for reconstitution

(6 µg / 4 µg/mL) x 1,000 = 1,500 µL

2.4 First briefly spin the Kininogen Standard vial to collect the contents on the bottom of the tube.

2.5 Reconstitute the Kininogen Standard vial by adding the appropriate calculated amount VD of

1X Diluent N to the vial to generate the 4 µg/mL Kininogen Standard #1.

Mix gently and thoroughly.

2.6 Allow the reconstituted 4 µg/mL Kininogen Standard #1 to sit for 10 minutes with gentle agitation prior to making subsequent dilutions

2.7 Label six tubes #2-7.

2.8 Add 120 µL of 1X Diluent N to tube #2 – 7.

2.9 To prepare Standard #2, add 120 µL of the Standard #1 into tube #2 and mix gently.

2.10 To prepare Standard #3, add 120 µL of the Standard #2 into tube #3 and mix gently.

2.11 Using the table below as a guide, prepare subsequent serial dilutions.

2.12 1X Diluent N serves as the zero standard, 0 µg/mL (tube #7)

Standard Dilution Preparation Table

Standard #	Volume to Dilute (µL)	Volume Diluent N (µL)	Total Volume (µL)	Starting Conc. (µg/mL)	Final Conc. (µg/mL)
1	**Step 10.1**				**4.000**
2	**120**	**120**	**240**	**4.000**	**2.000**
3	**120**	**120**	**240**	**2.000**	**1.000**
4	**120**	**120**	**240**	**1.000**	**0.500**
5	**120**	**120**	**240**	**0.500**	**0.250**
6	**120**	**120**	**240**	**0.250**	**0.125**
7	**-**	**120**	**120**	**-**	**0**

3 SAMPLE PREPARATION

3.1 Plasma

Collect plasma using one-tenth volume of 0.1 M sodium citrate as an anticoagulant. Centrifuge samples at 3,000 x g for 10 minutes. Dilute samples 1:200 into 1X Diluent N and assay. The undiluted samples can be stored at -20°C or below for up to 3 months. Avoid repeated freeze-thaw cycles. (EDTA or Heparin can also be used as an anticoagulant.).

3.2 Serum

Samples should be collected into a serum separator tube.

After clot formation, centrifuge samples at 3,000 x g for

10 minutes and remove serum. Dilute samples 1:200 into 1X Diluent N and assay. The undiluted samples can be stored at -20°C or below for up to 3 months. Avoid repeated freeze-thaw cycles.

4 PLATE PREPARATION

- The 96 well plate strips included with this kit are supplied ready to use. It is not necessary to rinse the plate prior to adding reagents.
- Unused well plate strips should be returned to the plate packet and stored at 4°C.
- For statistical reasons, we recommend each sample should be assayed with a minimum of two replicates (duplicates).
- Well effects have not been observed with this assay. Contents of each well can be recorded on the template sheet included in the Resources section.

5 ASSAY PROCEDURE

- Equilibrate all materials and prepared reagents to room temperature (18-25°C) prior to use.
- It is recommended to assay all standards, controls and samples in duplicate.

5.1 Prepare all reagents, working standards and samples as instructed. Equilibrate reagents to room temperature before use. The assay is performed at room temperature (18-25°C).

5.2 Remove excess microplate strips from the plate frame and return them immediately to the foil pouch with desiccant inside. Reseal the pouch securely to minimize exposure to water vapor and store in a vacuum desiccator.

5.3 Add 25 µL of Kininogen Standard or sample per well.

5.4 Add 25 µL of 1X Biotinylated Kininogen to each well. Cover wells with a sealing tape and incubate for two hours at room temperature. Start the timer after the last sample addition.

5.5 Wash five times with 200 µL of 1X Wash Buffer manually. Invert the plate each time and decant the contents; tap it 4-5 times on absorbent paper towel to completely remove the liquid. If using a machine wash six times with 300 µL of 1X Wash Buffer and then invert the plate, decant the contents; tap it 4-5 times on absorbent paper towel to completely remove the liquid..

5.6 Add 50 µL of 1X SP Conjugate to each well and incubate for 30 minutes. Turn on the microplate reader and set up the program in advance.

5.7 Wash microplate as described above.

5.8 Add 50 µL of Chromogen Substrate per well and incubate for about 20 minutes or till the optimal blue colour density develops. Gently tap plate to ensure thorough mixing and break the bubbles in the well with pipette tip.

ASSAY PROCEDURE

5.9 Add 50 µL of Stop Solution to each well. The color will change from blue to yellow.

5.10 Read the absorbance on a microplate reader at a wavelength of 450 nm immediately. If wavelength correction is available, subtract readings at 570 nm from those at 450 nm to correct optical imperfections. Otherwise, read the plate at 450 nm only. Please note that some unstable black particles may be generated at high concentration points after stopping the reaction for about 10 minutes, which will reduce the readings.

D-Dimer

ZYMUTEST DDimer (ARK023A)

Tested plasma or sample or controls:

The plasma sample was diluted fifty fold in the Sample diluent and using the DDimer calibrator (CAL) provided the following standards were used.

DDimer concentration	**C**	**C/2**	**C/4**	**C/10**	**C/20**	**0**
Vol. of Plasma DDimer calibrator	1 ml	0.5 ml	0.25 ml	0.1 ml	0.05 ml	0 ml
Vol. of Sample Diluent	0 ml	0.5 ml	0.75 ml	0.9 ml	0.95 ml	1 ml

Assay procedure:

Reagent	Volume	Procedure
DDimer Calibrator or tested sample or controls diluted 1:50 or -Sample Diluent (blank)	200 µl	Introduce the standard solutions, or the tested samples or the sample diluent, in the corresponding micro ELISA plate well.
Incubate for 1 hour at room temperature (18-25°C) (a)		
Wash Solution (20 fold diluted in distilled water)	300 µl	Proceed to 5 successive washings using the washing instrument (b).
Conjugate (anti DDimer monoclonal antibody coupled	200 µl	Introduce the Anti-(H)-DDimer - HRP immunoconjugate in the micro ELISA plate wells (b).

with peroxidase. Restored with 7.5 ml of conjugate diluent)		
Incubate for 1 hour at room temperature (18-25°C) (a)		
Wash Solution (20 fold diluted in distilled water)	300 µl	Proceed to 5 successive washings using the washing instrument (b).
TMB/H_2O_2 Substrate	200 µl	Immediately after the washing, introduce the substrate into the wells. The substrate distribution, row by row, must be accurate and at exact time intervals (b, c).
Incubate for exactly 5 minutes at room temperature (18-25 °C) (a)		
0.45M Sulfuric Acid	50 µl	Following exactly the same time intervals than for the addition of substrate, stop the colour development by introducing the 0.45M sulfuric acid (c).
Wait for **10 minutes** in order to allow the colour to stabilize and measure absorbance at **450 nm (A450)**		

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