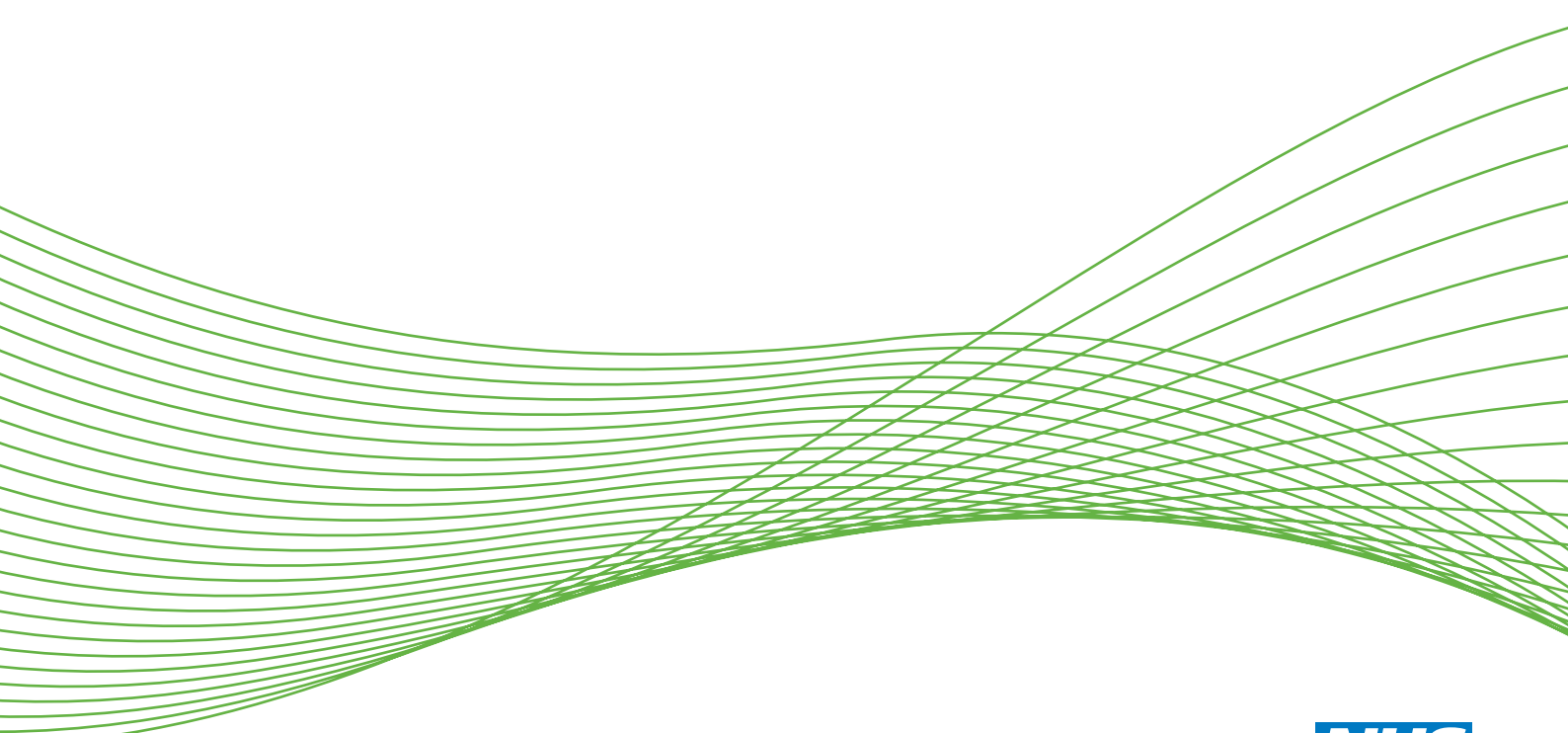


Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness

SG Thompson, LC Brown, MJ Sweeting, MJ Bown, LG Kim, MJ Glover, MJ Buxton, JT Powell and the RESCAN collaborators



***National Institute for
Health Research***

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Abstract

Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness

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Background: Small abdominal aortic aneurysms (AAAs; 3.0–5.4 cm in diameter) are usually asymptomatic and managed by regular ultrasound surveillance until they grow to a diameter threshold (commonly 5.5 cm) at which surgical intervention is considered. The choice of appropriate surveillance intervals is governed by the growth and rupture rates of small AAAs, as well as their relative cost-effectiveness.

Objectives: The aim of this series of studies was to inform the evidence base for small AAA surveillance strategies. This was achieved by literature review, collation and analysis of individual patient data, a focus group and health economic modelling.

Data sources: We undertook systematic literature reviews of growth rates and rupture rates of small AAAs. The databases MEDLINE, EMBASE on OvidSP, Cochrane Central Register of Controlled Trials 2009 Issue 4, ClinicalTrials.gov, and controlled-trials.com were searched from inception up until the end of 2009. We also obtained individual data on 15,475 patients from 18 surveillance studies.

Review methods: Systematic reviews of publications identified 15 studies providing small AAA growth rates, and 14 studies with small AAA rupture rates, up to December 2009 (later updated to September 2012). We developed statistical methods to analyse individual surveillance data, including the effects of patient characteristics, to inform the choice of surveillance intervals and provide inputs for health economic modelling. We updated an existing health economic model of AAA screening to address the cost-effectiveness of different surveillance intervals.

Results: In the literature reviews, the mean growth rate was 2.3 mm/year and the reported rupture rates varied between 0 and 1.6 ruptures per 100 person-years. Growth rates increased markedly with aneurysm diameter, but insufficient detail was available to guide surveillance intervals. Based on individual surveillance data, for each 0.5-cm increase in AAA diameter, growth rates increased by about 0.5 mm/year and rupture rates doubled. To control the risk of exceeding 5.5 cm to below 10% in men, on average a 7-year surveillance interval is sufficient for a 3.0-cm aneurysm, whereas an 8-month interval is necessary for a

5.0-cm aneurysm. To control the risk of rupture to below 1%, the corresponding estimated surveillance intervals are 9 years and 17 months. Average growth rates were higher in smokers (by 0.35 mm/year) and lower in patients with diabetes (by 0.51 mm/year). Rupture rates were almost fourfold higher in women than men, doubled in current smokers and increased with higher blood pressure. Increasing the surveillance interval from 1 to 2 years for the smallest aneurysms (3.0–4.4 cm) decreased costs and led to a positive net benefit. For the larger aneurysms (4.5–5.4 cm), increasing surveillance intervals from 3 to 6 months led to equivalent cost-effectiveness.

Limitations: There were no clear reasons why the growth rates varied substantially between studies. Uniform diagnostic criteria for rupture were not available. The long-term cost-effectiveness results may be susceptible to the modelling assumptions made.

Conclusions: Surveillance intervals of several years are clinically acceptable for men with AAAs in the range 3.0–4.0 cm. Intervals of around 1 year are suitable for 4.0–4.9-cm AAAs, whereas intervals of 6 months would be acceptable for 5.0–5.4-cm AAAs. These intervals are longer than those currently employed in the UK AAA screening programmes. Lengthening surveillance intervals for the smallest aneurysms was also shown to be cost-effective. Future work should focus on optimising surveillance intervals for women, studying whether or not the threshold for surgery should depend on patient characteristics, evaluating the usefulness of surveillance for those with aortic diameters of 2.5–2.9 cm, and developing interventions that may reduce the growth or rupture rates of small AAAs.

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List of abbreviations

AAA	abdominal aortic aneurysm	n	sample size
ACE	angiotensin-converting enzyme	NAAASP	NHS Abdominal Aortic Aneurysm Screening Programme
BMI	body mass index		
CENTRAL	Cochrane Central Register of Controlled Trials	NICE	National Institute for Health and Care Excellence
CI	confidence interval	ONS	Office for National Statistics
CT	computerised tomography	OR	odds ratio
EVAR	endovascular aneurysm repair	PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
HDU	high-dependency unit	PSA	probabilistic sensitivity analysis
HR	hazard ratio		
ICER	incremental cost-effectiveness ratio	QALY	quality-adjusted life-year
ICU	intensive care unit	RCT	randomised controlled trial
IPD	individual patient data	SD	standard deviation
IQR	interquartile range	SE	standard error
MASS	Multicentre Aneurysm Screening Study	UKSAT	United Kingdom Small Aneurysm Trial
MCMC	Markov chain Monte Carlo	US	ultrasound

Scientific summary

Background

Small abdominal aortic aneurysms (AAAs; 3.0–5.4 cm in diameter) are usually asymptomatic and managed by regular ultrasound surveillance until they grow to a diameter threshold (commonly 5.5 cm) at which surgical intervention is considered. The choice of appropriate intervals for surveillance is governed by the growth and rupture rates of small AAAs. Growth rates increase with AAA diameter, vary between people and may depend to an extent on patient characteristics. Rupture rates for small AAAs are considered to be low, but there is little evidence to quantify this and how they depend on AAA diameter and patient characteristics. The intervals between surveillance scans should be chosen to control to acceptable levels both the risk of rupture and the risk of growth to a size where surgery is indicated.

Various rescanning intervals are used in different surveillance programmes. Currently, in the NHS Abdominal Aortic Aneurysm Screening Programme (NAAASP) for men aged 65 years, yearly intervals are employed for 3.0–4.4-cm AAAs and 3-month intervals for 4.5–5.4-cm AAAs. These choices were based on the intervals used in the large UK Multicentre Aneurysm Screening Study (MASS) randomised trial of men aged 65–74 years, which showed that AAA screening reduced AAA-related mortality by about a half and was very cost-effective. Whether or not these intervals are optimal is not known, as there are no direct comparisons of different surveillance policies. However, changing these intervals would influence both effectiveness and costs. For example, lengthening the intervals would reduce surveillance costs, but would slightly increase AAA ruptures leading to both greater mortality and increased costs through emergency surgery. The best choice of surveillance intervals needs to take this balance into account.

Objectives

The aim of this series of studies was to inform the evidence base for choice of appropriate surveillance intervals for small AAAs. This was first attempted by (i) a systematic literature review of published small AAA growth rates and (ii) a systematic literature review of published small AAA rupture rates. Since published information proved insufficient for detailed modelling of small AAA growth and rupture rates, the project proceeded with (iii) analysis of individual patient data (IPD) from existing surveillance programmes, (iv) use of these IPD to investigate individual characteristics associated with growth and rupture rates, and to provide inputs for health economic modelling, and (v) development of a cost-effectiveness modelling framework to assess the impact of different surveillance intervals on costs, life expectancy and costs per quality-adjusted life-year (QALY) gained.

Methods

The databases MEDLINE, EMBASE on OvidSP, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and controlled-trials.com were searched from inception up until to the end of 2009. A systematic review of small AAA growth rates in published studies identified 61 potentially eligible reports. Detailed review yielded 15 studies providing growth rates for aneurysms of 3.0–5.5 cm in diameter (14 expressed as mm/year, one as percentage change/year). Additional studies published up to September 2012 were also reviewed.

Similarly, a systematic review of small AAA rupture rates in published studies identified 54 potentially eligible reports. There were only 14 studies from which rupture rates (as ruptures per 100 person-years) were available. Additional studies published up to September 2012 were also reviewed.

We obtained IPD on 15,475 patients under surveillance for small AAA from 18 studies, harmonised the data sets and developed novel statistical methods for their analysis. Individual AAA diameters in each study were analysed using a random-effects model that allowed for between-patient variability in size and growth rates. Rupture rates were analysed by joint proportional hazards regression to incorporate the modelled AAA diameter as a time-varying covariate. Predictions of the risks of exceeding 5.5 cm in diameter, and of rupture, within given time intervals were estimated, and pooled across studies in a second stage using random-effects meta-analysis. Acceptable risks were informed by the views of a focus group.

The influence of covariates (including demographics, medical and drug history) on aneurysm growth and rupture rates was investigated in each IPD surveillance data set. Growth rates were analysed using longitudinal random-effects modelling and rupture rates by Cox proportional hazards regression with adjustment for aneurysm diameter. The effects of covariates were combined across studies in a second stage using random-effects meta-analysis.

To perform the cost-effectiveness analyses, we first updated the original health economic model of AAA screening based on 4-year follow-up data in the MASS trial to employ the 10-year follow-up data now available, undertaking internal validation and parameter recalibration. We then modified the modelling framework to incorporate unobserved 'tunnel' states to allow the investigation of different surveillance intervals. Up-to-date (2010–11) unit costs were estimated for screening, surveillance, and elective and emergency surgery, drawing on data from various sources. We also incorporated data from NAAASP on the prevalence, attendance rate and distribution of AAA sizes at screening. Finally, we derived transition rates for AAA growth and rupture applicable to modelling different surveillance intervals from bespoke analyses of the 18 IPD surveillance data sets. We used a threshold value of £20,000 per QALY gained to calculate net benefit.

Results

In the systematic literature review of growth rates, the 15 studies included 7630 persons (predominantly male) enrolled during 1976–2005. The pooled mean growth rate was 2.32 mm/year [95% confidence interval (CI) 1.95 to 2.70 mm/year] but there was very high heterogeneity between studies, with average growth rates ranging from –0.33 to +3.95 mm/year. Six studies reported growth rates by 5-mm-diameter bands, which showed the trend for growth rate to increase with aneurysm diameter. Naive methods to estimate linear growth rates (such as last measurement minus first measurement/time interval) were associated with higher growth rate estimates. Meta-regression analysis showed that a 1-cm increase in aneurysm diameter was associated with a 1.62 mm/year [standard error (SE) = 0.20] increase in growth rate. Neither mean age nor percentage of women in each study had a significant effect. On average, a 3.5-cm aneurysm would take 6.2 years to reach 5.5 cm, whereas a 4.5-cm aneurysm would take only 2.3 years.

Detailed review of the 54 studies identified in the systematic literature review of rupture rates showed that ascertainment of rupture, patient follow-up and causes of death were poorly reported. Diagnostic criteria for rupture were never reported. The 14 studies in which rupture rates were available included 9779 patients (89% male) over the time period 1976–2006, but only seven of these studies provided rupture rates specifically for the AAA diameter range 3.0–5.5 cm. These ranged from 0 to 1.61 ruptures per 100 person-years.

In the analysis of IPD data sets, growth and rupture rates varied considerably between studies. For each 0.5-cm increase in AAA diameter, growth rates increased on average by about 0.5 mm/year and rupture rates doubled. For a 3.0-cm AAA the average growth rate in men was 1.3 mm/year (95% CI 1.0 to 1.5 mm/year), and for a 5.0-cm AAA it was 3.6 mm/year (95% CI 3.3 to 3.9 mm/year); the corresponding average rupture rates were 0.05 per 100 person-years (95% CI 0.03 to 0.07) and 0.64 (95% CI 0.43 to 0.95). To control the risk of exceeding 5.5 cm to below 10% in men, on average a 7-year surveillance interval

is sufficient for a 3.0-cm aneurysm, whereas an 8-month interval is necessary for a 5.0-cm aneurysm. To control the risk of rupture to below 1%, the corresponding estimated surveillance intervals are 9 years and 17 months.

Aneurysm growth rates were independent of age and sex. Average growth rates were higher in smokers (by 0.35 mm/year; $p < 0.001$) and lower in patients with diabetes (by 0.51 mm/year; $p < 0.001$). Mean arterial pressure had no effect and antihypertensive or other cardioprotective medications had only small, non-significant effects on aneurysm growth, consistent with the observation that calendar year of enrolment was not associated with growth rates. Rupture rates were almost fourfold higher in women than men ($p < 0.001$), doubled in current smokers ($p = 0.001$) and increased with higher blood pressure ($p = 0.001$), with some evidence that the aneurysm size had decreased over calendar time ($p = 0.03$).

Compared with the current surveillance policy in NAAASP, increasing the surveillance interval for the smallest aneurysms (3.0–4.4 cm) decreased costs and led to a positive net monetary benefit. For example, increasing the current 1-year interval to 2 years reduced costs by £2.57 and increased net monetary benefit by £1.33 per man invited to screening. Decreasing the interval from 1 year for these smallest aneurysms led to higher costs and a negative net benefit. For the larger aneurysms (4.5–5.4 cm), it was not similarly cost-effective to increase surveillance intervals from the current 3 months. For example, an increase to 6 months decreased costs by £1.51 but this was offset by a decrease in life expectancy so that the net benefit was only £0.10 per man invited to screening.

Conclusions

From the systematic reviews, we conclude that there is considerable variation between studies in the reported growth rates of small aneurysms beyond that explained by aneurysm diameter. Fuller evidence on which to base surveillance intervals for patients in screening programmes requires an IPD meta-analysis. We also conclude that rupture rates of small AAAs would appear to be low. However, most studies on rupture have been poorly reported and did not have clear ascertainment and diagnostic criteria for aneurysm rupture.

From the analysis of the IPD surveillance data sets, we conclude that surveillance intervals of several years are clinically acceptable for men with AAA diameters in the range of 3.0 to 4.0 cm. Intervals of around 1 year are suitable for 4.0–4.9-cm AAAs, whereas intervals of 6 months are appropriate for 5.0–5.4-cm AAAs. These intervals are longer than those currently employed in the UK AAA screening programmes. Recommendations for frequency of surveillance of individual patients could also consider diabetes and smoking, in addition to aneurysm diameter, but this would be difficult to organise in practice. Nevertheless, information given to patients who continued smoking is likely to increase both growth and rupture rates may be helpful in persuading them to quit. Our data also indicate differing risk factors for growth and rupture and suggest that a lower threshold for surgical intervention in women than men may be justified. No single class of drug used for cardiovascular risk reduction, including statins, was shown to have a major effect on the growth or rupture rate of small aneurysms.

Our cost-effectiveness investigations showed that lengthening the surveillance intervals from 1 year for 3.0–4.4-cm AAAs was cost-effective. However, the differences in costs were small, up to about £4 within an overall cost of £300 per man invited to AAA screening. Lengthening the 3-month interval for 4.5–5.4-cm AAAs to 6 months was neutral in terms of cost-effectiveness. Our results may be susceptible to the detailed modelling assumptions made and parameter estimates used, and the fact that our updated health economic model did not validate very well on the 10-year MASS trial data. Nevertheless, the cost-effectiveness analyses support some lengthening of surveillance intervals for the smallest aneurysms, in line with the clinical conclusions above.

Research implications

We draw the following conclusions about future research priorities:

- We identified that the definition and diagnostic criteria of AAA rupture were poorly reported in published studies. There is a need for standardised definitions and reporting, so that rupture rates can be more reliably estimated.
- We observed large variation in growth rates between studies, which was largely unexplained. The identification of both methodological reasons, for example how AAA diameters are measured, and biological causes for this variation are important. The latter could lead to the identification of factors and biological pathways related to increased growth rates or rupture rates that were amenable to intervention. Such interventions should then be assessed in randomised trials.
- We have shown that the clinical progression of AAA is different in women compared with men, with women at substantially higher risk of rupture. Currently, women are not screened for AAA in the UK and those with opportunistically detected AAA are usually entered into generic rather than sex-specific surveillance programmes. In addition to obtaining evidence to investigate the efficacy and cost-effectiveness of AAA screening in women, surveillance programmes and criteria for considering surgery need to be tailored for women.
- Although we have provided evidence about appropriate surveillance intervals for small AAAs, we have always used the currently accepted diameter of 5.5 cm for considering elective surgery. Related research could aim to determine whether or not it is possible to develop personalised criteria or patient-specific thresholds for elective surgery.
- Comparable studies with data sets of substantial size are required for the kind of research undertaken here. Future research should focus on the collection and use of large, well-structured and internationally compatible data sets, along with statistical and epidemiological methods needed for their harmonisation and analysis. The recent inception of national AAA screening programmes in several countries may facilitate such research.

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Chapter 1 Background

Abdominal aortic aneurysm screening

Abdominal aortic aneurysm (AAA) is an important cause of mortality, with around 4500 deaths each year in England and Wales.¹ Death due to an AAA usually occurs as a result of rupture, the overall survival rate from which is only about 20%.^{2,3} AAAs are usually asymptomatic until rupture occurs, but can be detected by ultrasound (US) screening. Following detection of an AAA (aortic diameter of at least 3.0 cm), either through screening or incidentally, the principal surgical strategy is to repair the AAA before rupture occurs. However, elective open AAA repair is associated with a mortality rate in the region of 5%.⁴ Although minimally invasive endovascular techniques can reduce this operative risk to < 2%,⁵ late complications make the long-term outcomes similar whatever operative method is chosen.⁶

The evidence in favour of screening older men for an AAA by US has come from four population-based randomised trials in different countries, with the evidence being summarised in a Cochrane review.⁷ In men, offering screening reduces aneurysm-related mortality by almost half [odds ratio (OR) 0.60, 95% confidence interval (CI) 0.47 to 0.78]. The data in women are too few to draw conclusions. Longer-term (10-year) follow-up of men randomised in the large UK Multicentre Aneurysm Screening Study (MASS) confirms a continued reduction in aneurysm-related mortality and indicates that offering screening is cost-effective within a 10-year time horizon.⁴ Long-term modelling based on the MASS trial suggests that the lifetime cost-effectiveness of a policy of offering screening to men aged 65 years is very favourable, with an estimated incremental cost-effectiveness ratio (ICER) of £2970 (95% CI £2030 to £5430) per quality-adjusted life-year (QALY) saved.⁸ Following this evidence, a national AAA screening programme for men aged 65 years was initiated in the UK.⁹ However, any national AAA screening programme must have clear policies for intervention and surveillance protocols. Such policies will depend, in a large part, on the growth rate and rupture rate of small aneurysms.

Surveillance for small abdominal aortic aneurysms

The two UK AAA screening trials used diameters of either 5.5 cm or 6.0 cm, as measured by US, as the threshold for considering elective surgery, whereas the Danish screening trial used a threshold of 5.0 cm and in the Australian screening trial the intervention threshold was decided by local vascular surgeons.⁷ A 5.5-cm threshold is being used in the UK NHS National Abdominal Aortic Aneurysm Screening Programme (NAAASP).⁹

Screening programmes identify AAAs with a wide range of diameters, but the majority (about 90%) have diameters < 5.5 cm.¹⁰ The evidence about managing these 'small' aneurysms has come from four randomised trials of intervention by open or endovascular surgical repair compared with surveillance for aneurysms 4.0–5.4 cm in diameter.¹¹ These trials did not show a survival benefit associated with a policy of early surgery below the 5.5-cm-diameter threshold, even after prolonged follow-up.¹² One reason that these trials have not shown a survival benefit is because the risk of rupture is very low while the aneurysm is still small.

The majority of small AAAs grow relatively slowly, but there is substantial variation in growth rates between different individuals.¹³ To prevent undetected progression of an AAA to a size where there is a high risk of rupture, repeated radiological scanning is necessary. Most patients with small AAAs require surveillance for many years and undergo multiple AAA measurements.

There is no randomised trial comparing different surveillance protocols, and no recent systematic review of the growth and rupture rates of small AAAs. As a result, screening and surveillance programmes in

different countries have adopted different intervals (*Table 1*), without a good evidence base for their choice. NAAASP employs surveillance intervals of 1 year for 3.0–4.4-cm AAAs and of 3 months for 4.5–5.4-cm AAAs. This choice corresponds to the intervals used in the large UK MASS trial, which has provided the majority of the randomised evidence worldwide (in terms of participants, person-years of follow-up and number of events) on the benefit of AAA screening.⁴

Growth rates of small abdominal aortic aneurysms

Apart from the screening trials, many other observational studies have reported on growth rates of small aneurysms and recommended different frequencies of follow-up examinations. Published studies report estimates of AAA growth in different ways, making them difficult to summarise. In addition, they only rarely report the variability in growth rates between patients, which is crucial for determining appropriate surveillance intervals.¹⁷ In many cases simple linear regression has been used to estimate growth rates. This does not account for the tendency for aneurysm growth to accelerate with increasing aneurysm diameter, nor for the bias introduced by termination of the available measurements after the threshold for surgical intervention is reached. Unbiased estimation of growth rates requires more complex statistical analysis using likelihood-based methods, for example based on multilevel modelling.¹³ Application of such analytical techniques shows that aneurysm growth rates vary considerably between people. Although most

TABLE 1 Small AAA surveillance intervals in different countries

Country	Diameter bands (cm)	Surveillance interval (months)	Source of information
Denmark	3.0–5.5	12	Stather <i>et al.</i> , 2013 ¹⁴
England ^a	3.0–4.4	12	NAAASP ⁹
	4.5–5.4	3	
Italy	3.0–3.9	12 ^b	Giardina <i>et al.</i> , 2011 ¹⁵
	4.0–4.9	6	
New Zealand	3.0–5.5	12	Stather <i>et al.</i> , 2013 ¹⁴
Norway	3.0–3.9	24	Stather <i>et al.</i> , 2013 ¹⁴
	4.0–4.5	12	
	4.5–5.5	3–6	
Sweden	2.5–2.9	60	Stather <i>et al.</i> , 2013 ¹⁴
	3.0–3.9	24	
	4.0–4.4	12	
	4.5–5.0	6	
	5.1–5.5	3	
USA	2.5–2.9	60	Chaikof <i>et al.</i> , 2009 ¹⁶
	3.0–3.4	36	
	3.5–4.4	12	
	4.5–5.4	6	

SVS, Society for Vascular Surgery (USA).

a Same intervals proposed for Northern Ireland, Scotland and Wales.

b Reported as 6 months by Stather *et al.*, 2013.¹⁴

aneurysms show a pattern of accelerating growth with increasing aneurysm diameter, some show a slowing of aneurysm growth, some linear growth, and some aneurysms even decrease in diameter over time.

Some studies report faster aneurysm growth in smokers and slower aneurysm growth in patients with diabetes, but evidence is inconsistent about sex differences.¹³ Two recent systematic reviews have addressed the efficacy of pharmacotherapy for decreasing aneurysm growth rates.^{18,19} These reviews concluded that, although beta blockers do not reduce growth rates, there is some promise that statins and other anti-inflammatory agents may reduce aneurysm growth rates. There is inconsistent evidence about the effect of blood pressure and other variables.

Rupture rates of small abdominal aortic aneurysms

The risk of rupture increases with AAA size. In patients with small aneurysms (< 5.5 cm in diameter), the risk of surgery is considered greater than the risk of rupture and a policy of surveillance is usually adopted. The low risk of rupture makes it difficult either to obtain reliable estimates of rupture rates of small aneurysms or to investigate how these rupture rates vary according to aneurysm size, sex and other patient characteristics. Reliable estimates of rupture rates are essential for planning the management of small aneurysms. Although some synthesis of data for rupture in large aneurysms has been reported previously,²⁰ systematic reviews and meta-analyses of studies focused on the rupture rate of small aneurysms (< 5.5 cm) have not been reported. Randomised trials have reported aneurysm rupture rates of 1% per annum or less for aneurysms of 4.0–5.5 cm in diameter.^{21,22} The rupture rate of smaller aneurysms appears to be even lower.²³

Need for systematic review and individual patient data analysis

To bring together the evidence on growth and rupture rates for small AAAs, a systematic review is required. However, individual studies publish their results in many different ways, making a quantitative synthesis problematic. This is compounded by the misuse of simple linear regression as an analysis tool, and by the selective (or lack of) information presented on how growth and rupture rates vary with patient characteristics. Thus, analysis of individual patient data (IPD) is likely to be necessary to obtain reliable estimates of small aneurysm growth and rupture rates, and for modelling the impact of different surveillance intervals.

Costs and cost-effectiveness

Different surveillance intervals lead to different associated costs, in terms of both the number of screens and the number of elective and emergency operations carried out. They also have different benefits in terms of life expectancy. Costs and benefits therefore have to be formally traded against each other by estimating the cost-effectiveness of different screening intervals, and expressing this as the incremental cost per QALY gained.

Overall aim of the project

This project has therefore sought to evaluate the available evidence pertinent to designing an evidence-based surveillance programme, by means of systematic reviews of the literature and analysis of IPD from surveillance studies. The choice of surveillance intervals should balance the frequency of rescreening intervals against their cost, and will depend on both aneurysm growth rates and aneurysm rupture rates. Although we focus on the UK context, and the NAAASP, our work clearly also has implications for other population-based screening and surveillance programmes.

Chapter 2 Research objectives

Aims and objectives

The overall aim is to synthesise the available evidence on the growth and rupture rates of small AAAs, in such a way that can inform the appropriate choice of surveillance intervals.

The following questions are addressed:

- What are the growth rates of small AAAs?
- What are the rupture rates of small AAAs?
- How does aneurysm size influence growth and rupture rates?
- How do other individual characteristics affect growth and rupture rates?
- What are the clinical implications of varying the surveillance intervals for small AAAs?
- What are the cost implications of varying the surveillance intervals for small AAAs?
- What is the incremental cost-effectiveness of changing the surveillance intervals from those currently implemented in the NAAASP?

To answer these questions we have:

1. conducted a systematic literature review of studies using US to monitor the growth of small AAAs
2. conducted a systematic literature review of the rates of rupture of small AAAs.

As this published information was not sufficient for detailed modelling of AAA growth and rupture rates, we then:

3. identified studies from these systematic reviews that could provide IPD to investigate AAA growth and rupture rates
4. collated and harmonised individual data from 18 surveillance studies
5. developed an extensive statistical modelling framework to analyse the growth rates of small AAAs by size and sex using likelihood-based multilevel modelling
6. undertook IPD meta-analyses of growth rates and of rupture rates
7. identified important patient characteristics associated with aneurysm growth and with aneurysm rupture
8. modelled surveillance intervals for persons identified with small AAAs, according to aneurysm size and sex.

We used bespoke statistical analyses from the IPD meta-analyses to provide inputs for health economic modelling, and:

9. developed an extended health economic modelling framework to estimate the incremental costs and cost-effectiveness of a range of surveillance strategies.

Structure of the report

Two systematic literature reviews were conducted: one of AAA growth rates and one of AAA rupture rates. The methods of these reviews are presented in *Chapter 3*, with results in *Chapter 4*. The protocols, search strategies and lists of excluded studies for these reviews are given in *Appendices 1* and *2*.

Under the name of the RESCAN Collaboration, IPD on small AAA surveillance were obtained from collaborating study groups. We collated data on both AAA diameters over time, to estimate growth rates, and ruptures. The collating and analysis of these data are described in *Chapter 5* (with detailed statistical methods in *Appendix 3*). The results, given in *Chapter 6*, are expressed in a way that is directly relevant to the choice of surveillance intervals for different sized aneurysms.

The cost implications of different surveillance strategies, and the comparative cost-effectiveness of using them in an AAA screening programme, are then studied. The methods used for this are given in *Chapter 7* (and additional details in *Appendix 4*), with results in *Chapter 8*.

Chapter 9 provides a discussion of all these component studies and conclusions are given in *Chapter 10*. A list of published papers arising from this work is provided in *Acknowledgements*.

Chapter 3 Methods for systematic reviews of growth and rupture rates

The project began with systematic literature reviews of small AAA growth rates and rupture rates. Their methods are described here (*Systematic literature review of small abdominal aortic aneurysm growth rates* and *Systematic literature review of small abdominal aortic aneurysm rupture rates*, respectively) and their results in *Chapter 4*.

Systematic literature review of small abdominal aortic aneurysm growth rates

Literature search

The systematic review followed quality reporting guidelines set by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) group (www.prisma-statement.org/).²⁴ A review protocol, that outlined every step of the systematic review, was developed (see *Appendix 1*). The protocol was reviewed and approved by one collaborator (FGRF).

The following databases were searched from inception up until the end of 2009 using search strategies shown in *Appendix 1*: MEDLINE, EMBASE on OvidSP, Cochrane Central Register of Controlled Trials (CENTRAL) 2009 Issue 4, ClinicalTrials.gov and controlled-trials.com. There were no filters used to restrict study designs, nor were there any language restrictions. In addition, reference lists were also searched for further studies to be included. Additional studies published up to September 2012 are discussed in *Chapter 9*.

Two researchers (JTP and SMG) independently reviewed potential studies according to a set of eligibility criteria. The studies (minimum sample size $n = 50$; men or women; aged ≥ 50 years) must include participants with a small infrarenal AAA (baseline anterior–posterior or transverse diameter of between 3.0 and < 6.0 cm) and with either serial US or computerised tomography (CT) scans assessed on at least two occasions separated by at least 6 months. Studies which encompassed wider diameter ranges were included provided growth rate estimates were available separately within the range of 3.0 to 5.5 cm. At this stage, to enable reading in house, languages were restricted to English, Spanish, French, Swedish, Danish and Norwegian. In addition, the following were excluded: review articles, studies in which patient data were duplicated (in which case the most recent or comprehensive study was used), non-human studies, editorials and letters (since they are often not peer reviewed), case reports, studies using patients previously treated by AAA surgery or aneurysms of other arteries, and studies reporting on patients with Marfan syndrome. Study authors were contacted in cases where aneurysms could not easily be separated according to size range.

Data extraction

A data extraction form to record variables and potential biases in the eligible studies was designed. In particular, the following were identified: the study design (prospective, retrospective, randomised, multicentre); source of patients (population screening, hospital screening); defined intervention policy; method of follow-up (US, CT); frequency of follow-up; patient recruitment (number of patients with two or more scans, excluded patients); presence of a mortality review committee; length of follow-up [mean, median, standard deviation (SD)]; inclusion criteria; recruitment period; trial using a particular drug; baseline data including age, sex, ethnicity and other cardiovascular risk factors (e.g. blood pressure, smoking status, drugs, ischaemic heart disease, peripheral arterial disease, diabetes); outcomes (how was aortic diameter measured, measurement variability, if growth was reported by size band, number of non-AAA deaths, number of AAA repairs, who carried out the aortic measurements); analysis (statistical methods used); author affiliation; date of publication; and country (where study was undertaken). The same two researchers

(JTP and SMG) independently extracted data of the potentially eligible primary studies and cross-checked their results. Any disagreements between the two reviewers were settled by a third person (LCB).

If any studies failed to provide essential variables (growth rates, frequency and length of patient follow-up) either the study was rejected or the study authors were contacted and asked to provide the missing data. If study authors did not respond to the reviewers' repeated correspondence, these studies were withdrawn from the selected publications. In addition, reasons for exclusion of particular studies were given.

Analysis

The reported overall mean growth rate (mm/year) and its standard error (SE) were extracted from each study, together with mean growth rates reported in size bands, by two statisticians (LCB and MJS). Median growth rates were used if means were not reported (3/15 studies). If percentage changes in AAA size were reported, these were converted to mean growth rates by using the mid-point of the reported size band.

Where 95% CIs were quoted in place of SEs, these values were converted by assuming normality and using the formula $SE = (UCL - LCL)/3.92$, where UCL and LCL are the upper and lower limits of the 95% CI. If a sample SD and number of patients (n) was quoted, then this was converted to a SE of the mean using the formula $SE = SD/\sqrt{n}$. If a 95% reference range was quoted, then this was first converted to a SD using the formula $SD = (URR - LRR)/3.92$, where URR and LRR are the upper and lower limits of the 95% reference range, and then to a SE of the mean, as above. Similarly, studies that reported interquartile ranges (IQRs) were first converted to SDs using the formula $SD = IQR/1.35$.

Studies that reported a number of different growth rates by size band (within the 3.0–5.5 cm range) but no overall growth rate were subjected to their own initial meta-analysis in which the size band estimates were pooled (using a fixed-effect meta-analysis) to obtain an additional overall growth rate estimate for that study. Studies with estimates from two treatment arms also were pooled in this way to obtain an overall study estimate. The overall estimates (one for each study) were then combined in a conventional random-effects meta-analysis.²⁵ Between-study heterogeneity was assessed using the I^2 measure,²⁶ which indicates the percentage of total variation across studies due to heterogeneity rather than chance.

Separate meta-analyses were also conducted for growth rates reported in 5-mm size bands in an attempt to account for some of the heterogeneity between study estimates. To account more comprehensively for heterogeneity due to varying AAA diameter ranges, a meta-regression model was fitted to the data using average AAA diameter as an explanatory variable.²⁷ Size band-specific estimates were included by using the mid-point of the size band as a proxy for average AAA diameter. Studies with only an overall estimate were included by using the mean baseline aneurysm diameter as the covariate value. A three-level model was then used to account for heterogeneity between studies, and between size bands within a study, after adjusting for average AAA diameter.²⁸ Average age and proportion of women in each study were also investigated as explanatory variables. All analyses were conducted using Stata version 11.0 (StataCorp LP, College Station, TX, USA) and R version 2.15.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Systematic literature review of small abdominal aortic aneurysm rupture rates

Literature search

The systematic review followed quality reporting guidelines set by the PRISMA group (www.prisma-statement.org/).²⁴ Therefore a review protocol, that outlined every step of the systematic review including exclusion criteria, was developed before starting the literature search and subsequent data extraction (see *Appendix 2*). The protocol was reviewed and approved by one collaborator (FGRF).

The databases MEDLINE, EMBASE on OvidSP, CENTRAL 2009 Issue 3, ClinicalTrials.gov and controlled-trials.com were searched from inception up until the end of 2009 using search strategies shown in *Appendix 2*.

Initially, there were no filters used to restrict study designs, nor were there any language restrictions. In addition, reference lists were also searched for further studies to be included. Additional studies published up to September 2012 are discussed in *Chapter 9*.

Two researchers (JTP and SMG) independently reviewed potential studies according to a set of eligibility criteria. Studies eligible for inclusion had participants (men or women, aged ≥ 50 years) with a small infrarenal AAA, spanning the baseline diameter range of between 3.0 and < 6.0 cm; for some studies this was a subgroup of the total patient group described. At this stage, languages were restricted to English, Spanish, French, Swedish, Danish and Norwegian (so that data could be extracted by the project team). In addition, review articles, studies in which patient data were duplicated (in which case the most recent or comprehensive study was used), non-human studies, editorials, letters, case reports, studies using patients previously treated by AAA surgery or aneurysms of other arteries, and studies reporting on patients with Marfan syndrome were all excluded.

There was no restriction on either the minimum number of ruptures or the timing when preceding aneurysm diameter measurements were recorded, although small studies of < 50 patients recruited over more than 3 years where rupture was not a primary outcome were excluded (because of probable patient selection and publication biases); although this proved never to be the sole reason for exclusion. In addition, study authors were contacted in cases where aneurysms could not easily be separated according to size range of interest. It also was essential that mean length or person-years of follow-up were reported in the eligible studies in order to calculate rupture rates; if these were not reported authors were contacted.

Data extraction

A data extraction form to record variables and potential biases in the eligible studies was designed. In particular, the following characteristics were identified: the study design; source of patients; defined intervention policy; method of follow-up; frequency of follow-up; patient recruitment; presence of a mortality review committee; length of follow-up (mean, median or total person-years); inclusion criteria; enrolment date; number of included patients (with more than one US scan or CT); age; sex; ethnicity; other baseline data (blood pressure, smoking status, drugs, ischaemic heart disease, peripheral artery disease, diabetes); outcomes (number of ruptures, how ruptures were diagnosed, whether or not ruptures were reported by size band, number of non-rupture deaths, number of AAA repairs, category of professional who carried out aortic measurements); analysis (statistical methods used); author affiliation; date of publication; and country (where study was undertaken). The same two researchers (JTP and SMG) independently extracted data from the eligible primary studies and cross-checked their results. Any disagreements between the two reviewers were settled by a third person (LCB).

Any studies that failed to provide essential variables (number of ruptures and length of follow-up) were either rejected or, if the study was published in the previous 15 years (1994–2009), the authors were contacted for this information. If study authors did not respond to the reviewers' repeated correspondence, these studies were withdrawn from the selected publications. The reasons for exclusion of studies are shown in *Appendix 2*.

Analysis

Rupture rates (per 100 person-years) were calculated from each study by extracting the number of reported ruptures and person-years of follow-up. For studies that reported mean follow-up, person-years were first calculated by multiplying the mean follow-up by the number of patients under surveillance. Any additional surveillance after aortic surgery was not included in the calculation of person-years. Rupture rates were estimated by dividing the number of ruptures by the person-years of follow-up and multiplying by 100. In addition, a small aneurysm rupture rate was calculated if the paper quoted the number of small aneurysm ruptures (last recorded measurement in the range of 3.0 to 5.5 cm) and person-years of follow-up in the small aneurysm range. This required the study to have recorded AAA diameter at regular intervals throughout follow-up, and crucially to have reported conditional follow-up within the diameter range of 3.0 to 5.5 cm. A 95% CI was calculated for each rupture rate by assuming the number of ruptures followed a Poisson distribution.

Chapter 4 Results of systematic reviews of growth and rupture rates

The results of the systematic reviews are presented here, in *Systematic review and meta-analysis of small abdominal aortic aneurysm growth rates* and in *Systematic review and meta-analysis of small abdominal aortic aneurysm rupture rates*.

Systematic review and meta-analysis of small abdominal aortic aneurysm growth rates

Identification of relevant studies

A total of 10,160 study titles were identified by the initial search strategy and, of these, 9951 were excluded after title searching (*Figure 1*). A total of 209 potential papers were selected, of which two had been identified by searching reference lists. In the next stage, abstracts were reviewed and 61 papers were selected for further review of full-text publications, while 148 were excluded. Of the eligible full-text publications, 46 were excluded for one or more of the following reasons: language ($n = 2$); duplicated data/patients ($n = 12$); no original data/data synthesis only ($n = 2$); growth rates not available/no longitudinal study ($n = 11$); selection criteria unspecified ($n = 1$); patient selection bias ($n = 8$); incorrect aneurysm size range ($n = 13$); no defined intervention policy ($n = 2$); too few patients ($n = 6$); growth rates not according to size range ($n = 2$); not restricted to AAA ($n = 1$); no frequency of follow-up ($n = 2$); and retrospective intervention policy ($n = 1$). A full list of excluded studies, with reasons, is provided in *Appendix 1*. Fifteen studies^{13,22,29–41} were identified as potentially eligible for inclusion in the systematic review and these are summarised in *Table 2*.

Study characteristics

The publication dates of the 15 potentially eligible studies^{13,22,29–41} ranged from 1994 to 2009, with patient recruitment from 1976 to 2005. Of these, 10 were prospective studies^{13,22,34–41} (including three randomised trials), four included both retrospective and prospective data^{29,30,32,33} and one study reported only retrospective data.³¹ Aneurysm growth was the primary outcome measure in 10 of the 15 studies. Overall, there were 7630 persons included in these 15 studies (although the two Spanish studies^{32,33} may have included some duplicated patients). Some studies did not report accurately on the sex of participants,^{30,34} but in those that did the proportion of women ranged from 0% to 24% of the study population. The mean baseline age ranged from 65 to 71 years, although age was not reported in two studies.^{29,30} The study size ranged from 134 to 1743 patients, with most patients followed up for between 1 and 5 years; not all of these studies stated the mean length of follow-up or patient-years of follow-up.

Most studies used US to monitor aortic diameter, but the plane and cursor positioning (internal vs. external) varied across the different studies and, for some studies, the precise plane of reference was not specified. Some studies used CT as well as US.^{22,29,33} Most of these studies included aortic diameters from 30 mm (at baseline), except three studies, which reported from either 25 mm^{31,35} or 28 mm.¹³ Not all studies restricted their reporting to the aneurysm diameter range of interest (3.0–5.5 cm) and in some instances substudies were identified, which reported on a more restricted range.^{13,29,33} Different methods were used to estimate aneurysm growth, usually reported as mm/year, with linear regression or (last–first diameter)/time being the most common; two studies did not report how they estimated aneurysm growth.^{29,36} One study only reported percentage changes in aneurysm diameter and used data from two screening programmes (Chichester and Huntingdon).³⁴ Two studies were more than 10 years old, so that requests to authors for further information met with little success. These and other details of the included studies are shown in *Table 2*. Quality indicators for both imaging and design of the 15 included studies^{13,22,29–41} are listed in *Table 3*.

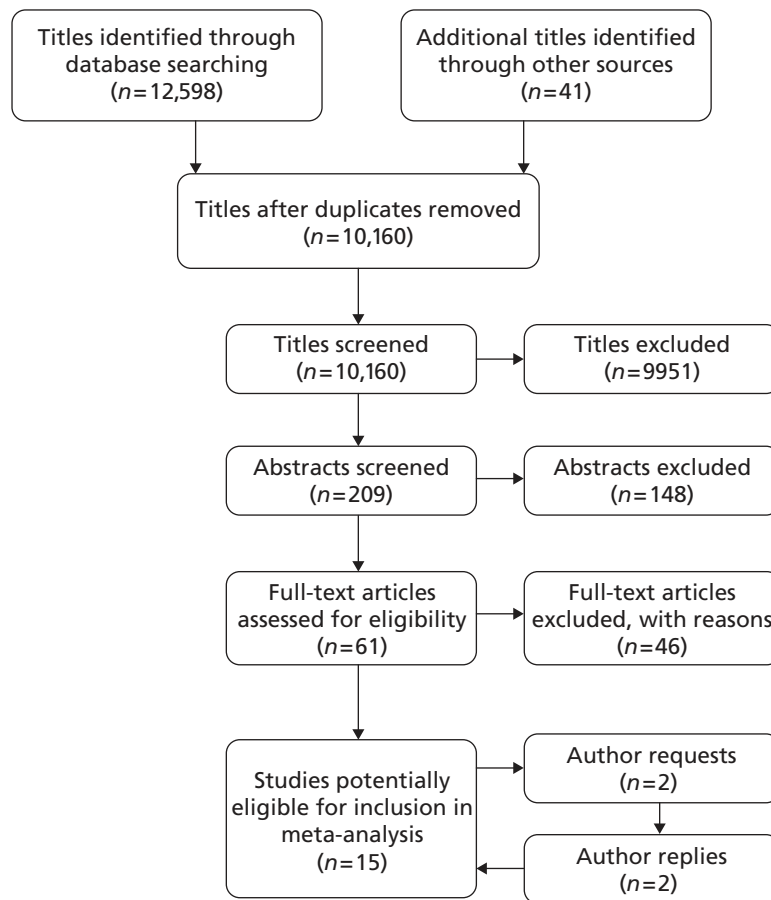


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram – small AAA growth studies.

Other patient characteristics, such as ethnicity, history of smoking, prevalence of diabetes, blood pressure, proportion of participants with ischaemic heart disease and peripheral arterial disease, were reported variably across the 15 studies.^{13,22,29–41}

Comparison of small aneurysm growth rates

Overall average growth rate estimates are shown in *Figure 2*, with separate estimates for the Huntingdon and Chichester studies.³⁴ There was very substantial heterogeneity between study estimates ($I^2 = 98\%$), with reported growth rates ranging from -0.33 mm/year to $+3.95$ mm/year. The Huntingdon study³⁴ was reported as having a negative growth rate and the largest growth rate was reported from a study which only included 40- to 49-mm-diameter aneurysms.³³ One study could not be included because no SE could be calculated from the information reported.³⁰ The random-effects meta-analysis estimate of the average aneurysm growth rate was 2.32 mm/year (95% CI 1.95 mm/year to 2.70 mm/year). Restriction of the meta-analysis to those studies that only used ultrasonography imaging after 1990 (reflecting potentially better imaging quality), the growth rate reduced slightly to 2.05 mm/year (95% CI 1.64 mm/year to 2.45 mm/year), although the heterogeneity remained high ($I^2 = 97\%$).

Rates are summarised in *Figure 3* for those studies that reported mean growth rates by 5-mm-diameter bands.^{29,32,35–38} Estimates within these size bands generally were more homogeneous than the overall estimates, although heterogeneity still remained (I^2 ranged from 11% to 91%). Growth rates increased steadily with aneurysm diameter band, with a pooled mean growth rate of 1.81 mm/year (95% CI 1.55 mm/year to 2.07 mm/year) for individuals whose baseline diameter measured 3.0–3.4 cm compared with 4.96 mm/year (95% CI 4.25 mm/year to 5.66 mm/year) for individuals whose baseline diameter

TABLE 2 Published growth rates of small AAAs (initial diameter of 3.0 to 5.5 cm)

Author, year	Country, enrollment dates	Number of patients (women)	Aortic diameter measured [mean baseline diameter (mm)]	US/CT	Frequency of follow-up (intervention threshold, if specified)	Length of follow-up	Method of growth rate estimation and reporting	Baseline AAA size range(s) (mm)	Growth rates reported in mm/year (SE)
Brady <i>et al.</i> , 2004 ¹³	UK, 1991–5	1743 (387)	Maximum external AP [43]	US	≥50 mm: every 3 months; <50 mm: every 6 months (5.5 cm)	3312 person-years	Method: random-effects models (linear, quadratic) Mean growth rates reported	Overall: 28–85 (n = 1743)	2.6 (0.03)
Brown <i>et al.</i> , 2003 ²⁹	Canada, 1976–2001	895 (207)	Not reported [40]	US (1976–82); CT (1983 onwards)	6-monthly	3088 person-years	Method: not reported Mean growth rates reported	Overall: 30–49 (n = 895) 30–34 (n = 191) 35–39 (n = 204) 40–44 (n = 306) 45–49 (n = 194)	3.8 (0.2) 2.8 (0.3) 3.4 (0.3) 4.5 (0.3) 5.2 (0.4)
Karlsson <i>et al.</i> , 2009 ³⁹	Sweden, 2002–5	211 (50)	Wider of the external AP and transverse [40 in both groups]	US	6-monthly	18–36 months	Method: linear regression Median growth rates reported	Overall: 35–49 (n = 211)	2.2 (0.1)
Propranolol Aneurysm Trial Investigators, 2002 ⁴⁰	Canada, 1993–8	548 (87)	External AP [38 in both groups]	US	6 months (5.0 or 5.5 cm by centre)	Mean 2.5 ± 1.1 years (range 0–4.5 years)	Method: unclear (last–first diameter)/time or linear regression Mean growth rates reported	Overall: 30–50 (n = 531) [Growth rate only calculated for 531 patients]	2.4 (0.1)
Lederle <i>et al.</i> , 2002 ²²	USA, 1992–6	567 (2)	Maximal external cross-sectional in any plane [47]	US; CT (baseline and ≥53 mm)	Every 6 months	Mean 3.0 years	Method: (last–first diameter)/time Median growth rate reported	Overall: 40–54 (n = 567)	3.2 (0.08)

continued

TABLE 2 Published growth rates of small AAAs (initial diameter of 3.0 to 5.5 cm) (continued)

Author, year	Country, enrolment dates	Number of patients (women)	Aortic diameter measured [mean baseline diameter (mm)]	US/CT	Frequency of follow-up (intervention threshold, if specified)	Length of follow-up	Method of growth rate estimation and reporting	Baseline AAA size range(s) (mm)	Growth rates reported in mm/year (SE)
Lindholt <i>et al.</i> , 2000 ³⁵	Denmark, 1994–8	151 (0)	Maximum external AP [mean diameter not reported]	US	Annually (5.0 cm)	1–5 years	Method: (last–first diameter)/time Mean growth rate reported	Overall: 30–49 (n=151)	2.8 (0.20)
McCarthy <i>et al.</i> , 2003 ³⁷	UK, 1990–2002	496 (0)	Maximum AP External A to internal P [34]	US	26–39 mm: 12 months; > 40 mm: 6 months (5.5 cm)	Mean 4.2 (SD 2.4) years	Method: (last–first diameter)/time Median growth rate reported	Overall: 30–39 (n=496)	1.9 (0.1)
Santilli <i>et al.</i> , 2002 ³⁶	USA, 1990–6	790 (0)	Wider of external AP and lateral [33]	US	At least one further scan > 90 days after initial scan (5.5 cm)	3071 person-years	Method: not reported Mean growth rates reported	Overall: 30–39 (n=790) 30–34 (n=578) 35–39 (n=212)	1.6 (0.07) 1.5 (0.08) 2.0 (0.13)
Scheve <i>et al.</i> , 1994 ³⁰	Germany, 1976–93	134 (not reported)	Mean of AP and transverse [37]	US	6 months	536 person-years (5.0 cm)	Method: (last–first diameter)/time Mean growth rates reported	30–39 (n=69) 40–49 (n=30) > 50 (n=11)	2.3 (no SE) 3.1 (no SE) 3.9 (no SE)
Schlosser <i>et al.</i> , 2008 ⁴¹	Holland, 1996–2005	147 (16)	AP diameter [39]	US	30–39 mm: 12 months; 40–55 mm: 6 months (5.5 cm)	Median 3.3 years (range 0.5–11.1 years) 599 person-years	Method: linear regression Mean growth rate reported	Overall: 30–55 (n=147)	2.5 (0.26)
Schouten <i>et al.</i> , 2006 ³¹	Holland, 2002–5	150 (24)	Maximum external AP [38]	US	6–12 months (5.0 cm)	Median 3.1 years	Method: linear regression Mean growth rate reported	Overall: 25–53 (n=150)	2.95 (0.23)

Author, year	Country, enrollment dates	Number of patients (women)	Aortic diameter measured [mean baseline diameter (mm)]	US/CT	Frequency of follow-up (intervention threshold, if specified)	Length of follow-up	Method of growth rate estimation and reporting	Baseline AAA size range(s) (mm)	Growth rates reported in mm/year (SE)
Solberg <i>et al.</i> , 2005 ³⁸	Norway, 1994–5	234 (49)	External transverse or AP [35]	US	Every 3 or 6 months	1212 person-years	Method: linear regression	Overall: 30 to >49 (n = 234)	1.82 (0.14)
							Mean growth rates reported	30–34 (n = 87)	1.80 (0.25)
								35–39 (n = 58)	1.75 (0.14)
								40–44 (n = 23)	2.31 (0.48)
								45–49 (n = 11)	3.36 (0.95)
								>49 (n = 9)	2.63 (1.57)
Vardulaki <i>et al.</i> , 1998 ³⁴	UK, Chichester 1983–96; Huntingdon 1991–6	Chichester: 519 men and women; Huntingdon: 498 men (0 women)	In Chichester the wider of AP and transverse measurements External AP in Huntingdon [mean diameters not reported]	US	3–12 months (Chichester: 6.0 cm initially; Huntingdon: 4.5 cm)	Chichester: mean 3.4 years Huntingdon: mean 2.3 years	Method: random-effects model based on exponential growth Percent change in growth rates reported	Chichester: Overall: 30 to ≥50 (n = 519) 40–49 Huntingdon: Overall: 30–49 (n = 498) 30–39 40–49	0.9 (0.1) 0.7 (0.2) 1.5 (0.4) 3.5 (0.7) –0.3 (0.2) –0.6 (0.3) 0.9 (0.6)

continued

TABLE 2 Published growth rates of small AAAs (initial diameter of 3.0 to 5.5cm) (continued)

Author, year	Country, enrollment dates	Number of patients (women)	Aortic diameter measured [mean baseline diameter (mm)]	US/CT	Frequency of follow-up (intervention threshold, if specified)	Length of follow-up	Method of growth rate estimation and reporting	Baseline AAA size range(s) (mm)	Growth rates reported in mm/year (SE)
Vega de Céniga <i>et al.</i> , 2006 ³²	Spain, 1988–2004	352 (19)	Wider of external AP and transverse [36]	US CT (for 40–49 mm)	Annually (group 30–39) 6-monthly (group 4.0–4.9) (5.0 cm)	Overall mean 55.2 ± 37.4 months (range 6.3–200 months)	Method: (last–first diameter)/time Mean growth rates reported	Overall: 30–49 (n = 352)	2.87 (0.23)
Vega de Céniga <i>et al.</i> , 2008 ³³	Spain 1998–2004	195 (12)	Wider of maximum external AP or transverse [42.5]	CT	6 months (5.0 cm)	Mean 50 ± 36.4 months (range 6.5–194 months)	Method: (last–first diameter)/time Mean growth rate reported	Overall: 40–49 (n = 195)	3.95 (0.43)

A, anterior; AC, author communication; AP, anterior–posterior; P, posterior.

a Patient group extended in Vega de Céniga *et al.*, 2008.³³

Studies listed by author in alphabetical order.

Figures shown in bold have been subsequently calculated from the published data using the methods described in the text.

measured 4.5–4.9 cm. The greater number of patients in the smaller diameter bands is one reason why the widths of the CIs increase with aneurysm diameter.

The statistical method used to calculate growth rates and the study design (retrospective or prospective) were significantly associated with growth rates. Studies that used hierarchical modelling or linear regression had, on average, growth rates that were respectively 1.52 mm/year (SE 0.51 mm/year) and 0.40 mm/year (SE 0.40 mm/year) smaller than studies that used (last–first diameter)/(time elapsed) to report growth rate. Prospective studies had, on average, growth rates that were 1.11 mm/year (SE 0.39 mm/year) smaller than either retrospective or partially retrospective designs, although this effect was no longer significant after adjusting for the method used to calculate growth rate.

A meta-regression with average aneurysm diameter as an explanatory variable resulted in a strong trend between diameter and growth rate (*Figure 4*). After adjusting for average diameter, between-study heterogeneity was estimated to be about twice that of the heterogeneity between estimates within a study. A 1-cm increase in AAA diameter was found to be associated with a 1.62 mm/year (SE 0.20 mm/year) increase in growth rate. The age and sex of included patients was available for nearly all studies and were assessed as explanatory variables but found to be not statistically significant; a 10% increase in the percentage of women in a study increased the growth rate by a modest 0.13 mm/year (SE 0.26 mm/year), whereas a 5-year increase in mean study participant age decreased the growth rate by 0.01 mm/year (SE 0.56 mm/year).

Based on the linear relation between growth rate and aneurysm diameter (see *Figure 4*), the size of aneurysms is expected to grow exponentially with time. Given the meta-regression relationship shown, aneurysms with diameters of 3.0, 3.5, 4.0, 4.5 and 5.0 cm would be expected, on average, to take 9.6, 6.2, 4.0, 2.3 and 1.1 years, respectively, to reach 5.5 cm.

However, there was insufficient published data for the detailed modelling of AAA growth rates necessary to better inform surveillance intervals. For this, IPD are necessary, as described in *Chapters 5 and 6*.

Systematic review and meta-analysis of small abdominal aortic aneurysm rupture rates

Identification of relevant studies

A total of 10,160 study titles were identified by the initial search strategy and, of these, 9951 titles were excluded (*Figure 5*). In the next step, a total of 209 potential abstracts were reviewed and 54 selected for further review of the full-text publication (155 were excluded). Of the 54 eligible full-text publications, 40 were excluded for the following reasons (see *Appendix 2*): (1) language ($n = 3$); (2) duplicated patients/data ($n = 7$); (3) modelling, no original data ($n = 5$); (4) person-years' follow-up not available ($n = 21$); (5) inaccurate diagnostic criteria of either aneurysm size or rupture ($n = 3$); (6) patient selection bias ($n = 6$); (7) ruptures in incorrect size range ($n = 11$); and (8) small studies (< 50 patients collected over more than 3 years) ($n = 4$). Some studies were excluded for more than one reason and some reasons were ascertained by author enquiry or after statistical review. A total of 14 eligible studies^{22,23,29,32,36,37,40–47} were identified for inclusion in the systematic narrative review and are shown in *Table 4*.

Study characteristics

The 14 included studies^{22,23,29,32,36,37,40–47} were published from 1991 to 2008 (with patients enrolled from 1976 to 2006); 11 of these were prospective studies^{22,23,29,32,36,37,40,41,43–45} (including four randomised trials), whereas the remaining three studies^{42,46,47} had both retrospective and prospective contributions. Only five of the studies had aneurysm rupture as a primary outcome measure^{23,41,43,45,46} and even in these studies the diagnostic criteria for aneurysm rupture were not reported. Overall, 9779 patients (8662 men, and 1117 women) were included, with study size ranging from 176 to 2257 patients and average length of follow-up ranging from 1.6 to 4.6 years. Most studies used US to monitor aortic diameter, but some studies used CT as well as US^{29,32,41,46,47} and one study also used magnetic resonance imaging.⁴⁷ Many studies included patients with

TABLE 3 Quality assessment of studies included in the systematic review

Quality aspect	Brady <i>et al.</i> , 2004 ¹³	Brown <i>et al.</i> , 2003 ²⁹	Karlsson <i>et al.</i> , 2009 ³⁹	Propranolol Aneurysm Trial Investigators, 2002 ⁴⁰	Lederle <i>et al.</i> , 2002 ²²	Lindholt <i>et al.</i> , 2000 ³⁵	McCarthy <i>et al.</i> , 2003 ³⁷
After 1990 (image quality)	Y	N	Y	Y	Y	Y	Y
Standardisation of imaging	Y	N	Y	Y	N	Y	Y
Variability of diameter given	Y	N	N	Y	For CT only	Y	N
Study type (P, R, PR)	P	PR	P	P	P	P	P
Study type (RCT/obs)	RCT + obs	Obs	RCT	RCT	RCT	RCT + obs	Obs
Inclusion to obs comprehensive	N	Y				N	Y
Intervention policy stated at start (diameter, cm)	Y (randomised at 4.0 or 5.5 ^a)	N	N	Y (either 5 or 5.5)	Y (randomised at 4.0 or 5.5 ^a)	Y (5.0)	Y (5.5)
Patient censorship defined	Y	N	Y	Y	Y	Y	Y

C, Chichester; H, Huntingdon; N, no; obs, observational study; P, prospective; PR, both prospective and retrospective; R; retrospective; RCT, randomised controlled trial; U, unclear; Y, yes.
 a To observation or surgery.

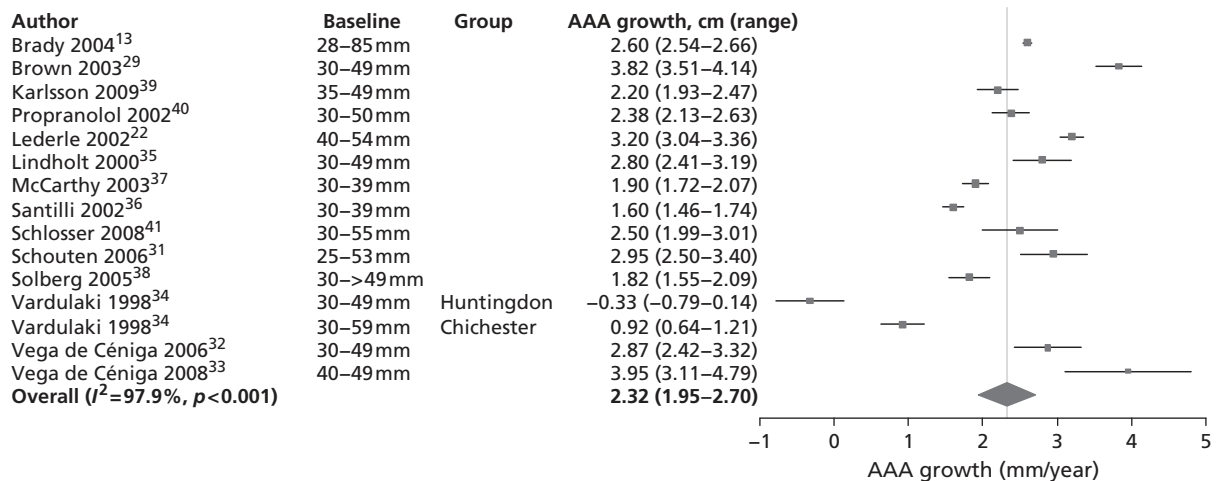


FIGURE 2 Overall AAA growth rate estimates, one for each study, by baseline AAA diameter size range. Estimates are pooled using a random-effects meta-analysis, due to considerable heterogeneity ($I^2 = 98\%$). An estimate from Schewe *et al.*³⁰ could not be included due to no SE being available.

Santilli <i>et al.</i> , 2002 ³⁶	Schewe <i>et al.</i> , 1994 ³⁰	Schlosser <i>et al.</i> , 2008 ⁴¹	Schouten <i>et al.</i> , 2006 ³¹	Solberg <i>et al.</i> , 2005 ³⁸	Vardulaki <i>et al.</i> , 1998 ³⁴		^a Vega de Céniga <i>et al.</i> , 2006 ³²	Vega de Céniga <i>et al.</i> , 2008 ³³
					C	H		
Y	N	Y	Y	Y	N	Y	N	Y
N	N	N	N	N	N	N	N	N
N	N	N	Y	N	N	N	N	N
P	PR	P	R	P	P	P	PR	PR
Obs	Obs	Obs	Obs	Obs	Obs	Obs	Obs	Obs
N	N	Y	N	N	U	U	Y	Y
Y (randomised at 4.0 or 5.5 ^a)	Y (5.0)	Y (5.5)	Y (5.0)	N	Y (6.0, later 5.5)	Y (4.5)	Y (5.0)	Y (5.0)
Y	N	Y	U	Y	Y	N	U	Y

aortas < 3.0 cm in diameter or with aneurysms > 5.5 cm in diameter and for many studies it was not clear if patients with aortas either < 3.0 cm or > 5.5 cm were included in the years of follow-up reported. Only one study⁴⁴ unambiguously reported conditional follow-up for the diameter range of 3.0 to 5.5 cm, although this could be estimated in six further studies.^{22,23,29,43,45,47} These seven studies comprised 5934 patients (86% male).^{22,23,29,43-45,47} Many studies were more than 10 years old, so that requests to authors for further information met with little success.

The diagnostic criteria for aneurysm rupture were not reported in any study and methods for the ascertainment of rupture were reported in only two studies;^{22,23} only these studies and one other⁴⁰ had any independent audit of deaths. One randomised trial²² reported 11 ruptures in the surveillance group; however, two cases were reported as being discovered at laparotomy for elective surgery (one as 'a hole in the aortic wall covered by a thin layer of connective tissue', the other as 'a hole plugged by thrombus'), rather than findings made on pre-operative imaging. This information was reviewed independently by two professors of vascular surgery; in the absence of information about intramural or extramural haematoma, their decision was that these two cases should not be considered as ruptures for the purposes of this review. Causes of death other than from aneurysm rupture were often not collected systematically and were reported variably, which might have led to under-reporting of aneurysm rupture rates in several studies (only three studies had any independent review of causes of death^{22,23,41}).

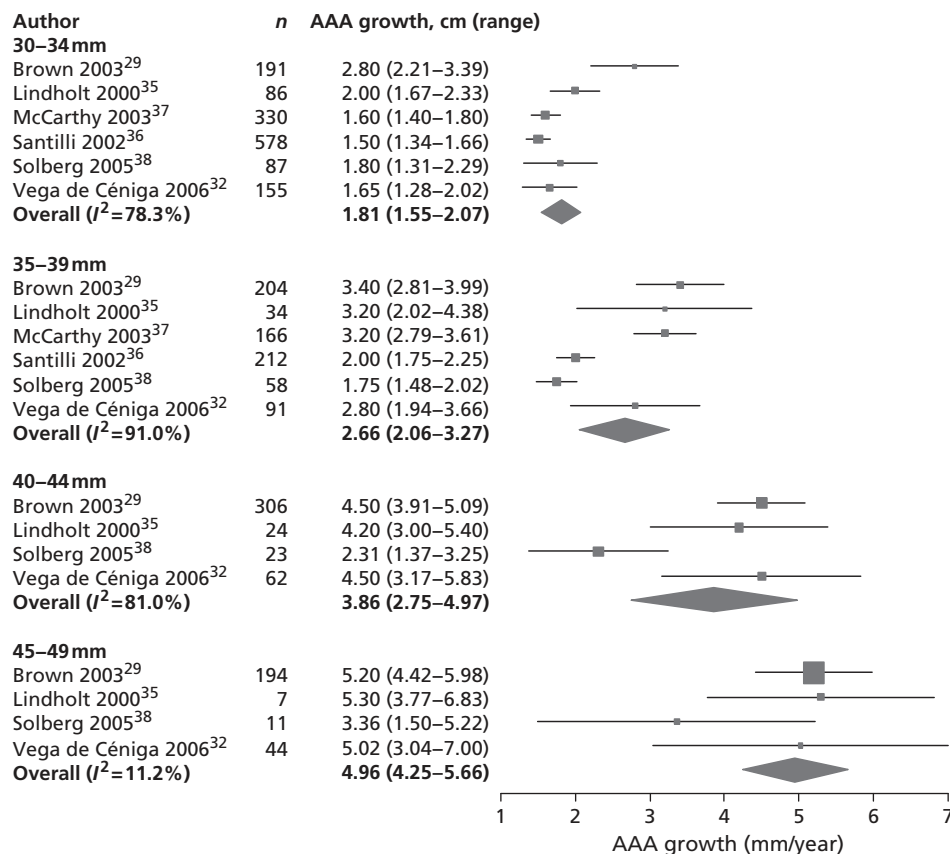


FIGURE 3 Aneurysm growth rate by 5-mm size ranges of baseline aneurysm diameter: random-effect meta-analyses conducted within subgroups.

The mean or median age of patients was reported as between 65 and 75 years in most of the included studies,^{22,23,29,32,36,37,40–43,45,46} but age was not specified in two studies.^{44,47} The majority of the studies included both sexes, although women were always in a minority. Three population-screening studies reported exclusively on male participants.^{36,37,44} Details of the included studies (e.g. age, inclusion criteria, description of study follow-up and intervention policy, last diameter and time between last diameter and rupture) are summarised in *Table 5*.

Other characteristics, such as ethnicity, history of smoking, prevalence of diabetes, blood pressure and other clinical history, were not available for all studies.

Comparison of small aneurysm rupture rates

The seven studies reporting on aneurysms in the baseline diameter range of 3.0 to 5.5 cm, and with follow-up restricted to this range (conditional follow-up to 5.5 cm in diameter, larger aneurysms excluded), provided rupture rates estimated as varying from 0 to 1.61 ruptures per 100 person-years (*Figure 6*). The studies in the figure are sorted according to the mid-point of the diameter range and exhibit a slight trend towards higher rupture rates for larger diameters (for example, no ruptures were reported within 12 months of a measurement of < 4.0 cm). Nevertheless, the size range only partly explains the considerable heterogeneity between the rupture rate estimates, demonstrated by an I^2 value of 89%. Two studies estimate the rupture rate to be greater than 1.0 rupture per 100 person-years,^{23,43} whereas the point estimates from the remaining five studies^{22,29,44,45,47} are all below 0.5 ruptures per 100 person-years. Owing to the large statistical and clinical heterogeneity, a formal synthesis of the results (meta-analysis) was not carried out.

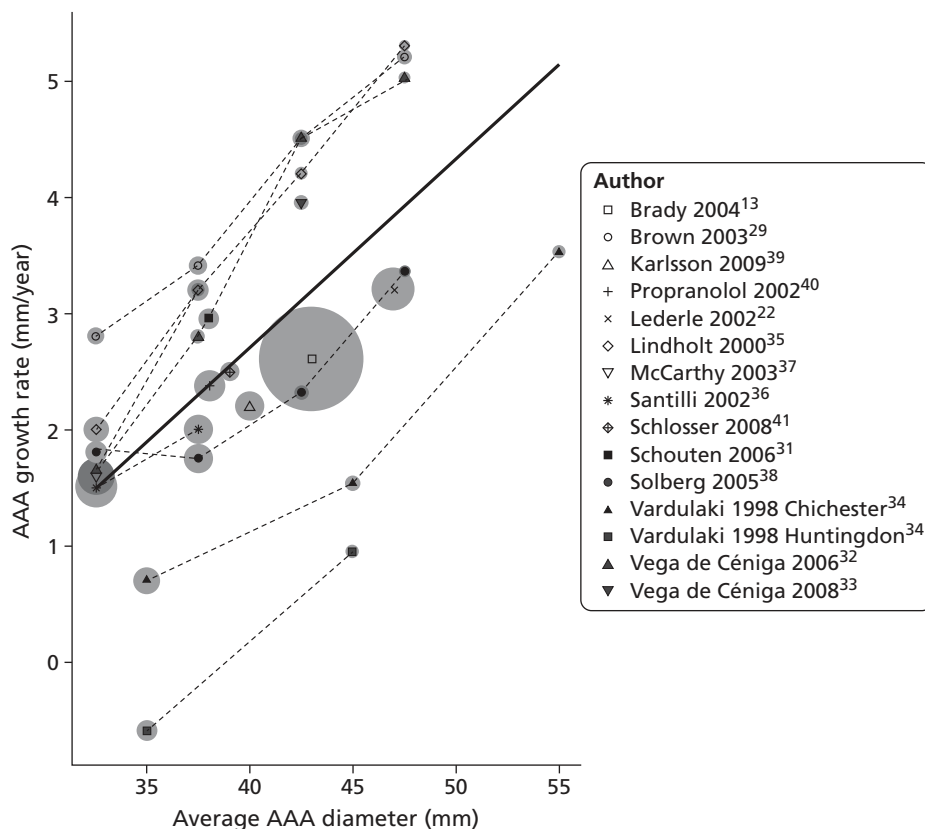


FIGURE 4 Meta-regression of AAA growth rate estimates by AAA diameter. The overall regression line is shown by the solid bold line. The mid-point of the reported size range is used to calculate AAA diameter for range-specific estimates, whereas the mean baseline diameter is used for overall estimates. Estimates from the same study are joined by a dotted line. The circles have an area in proportion to the amount of information (inverse variance of the estimate).

Rupture rates estimated from total reported ruptures and follow-up (including aneurysms > 5.5 cm) from all 14 studies^{22,23,29,32,36,37,40–47} (Figure 7) ranged from 0 to 2.51 ruptures per 100 person-years. In this figure, the studies are sorted according to the mid-point of the baseline diameter range. The between-study variation is even more extreme, with an I^2 value of 96%.

The published information on rupture rates is thus inadequate for the detailed modelling needed to inform surveillance intervals. For this, IPD are necessary, as described in *Chapters 5 and 6*.

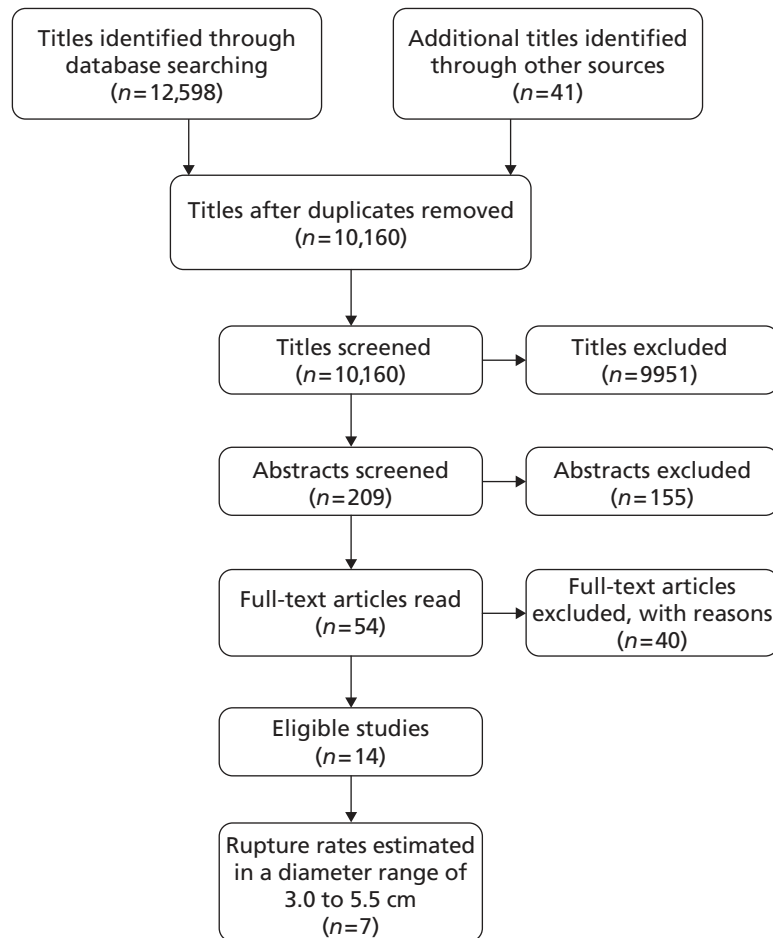


FIGURE 5 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram – small AAA rupture studies.

TABLE 4 Studies reporting on the rupture rate of small AAAs (3.0–5.5 cm in diameter)

Author, year and country	Total number of patients (women) [baseline AAA diameter]	Total ruptures per total person-years reported	Total small aneurysm ruptures per small aneurysm person-years [diameter range for subgroups] (fatal ruptures by 30 days)	Rate of small aneurysm ruptures per 100 person-years (95% CI)	Comments
Brown, 1999 ²³ UK	2257 (465) [3.0–9.7 cm]	103/4102	67/3215 [3.0–5.9 cm] 27/2600 [3.0–4.9 cm] (fatal NR) 40/615 [5.0–5.9 cm] (fatal NR)	2.08 (1.62 to 2.65) 1.04 (0.68 to 1.51) 6.50 (4.65 to 8.86)	1. Person-years for the 3.0–4.9 cm size range calculated from number of ruptures per reported rupture rate
Buckenham, 2007 ⁴² New Zealand	198 (50) [2.8–7.8 cm]	5/325.05	3/unknown (3 fatal)	Unknown	1. Threshold diameter for surgery changed from 5.5 cm to 5.0 cm in June 2004 2. Person-years estimated from median follow-up
Brown, 2003 ⁴³ Canada	372 (99) [5.0–5.4 cm]	9/560	9/560 [5.0–5.4 cm] (fatal NR)	1.61 (0.73 to 3.05)	
Scott, 2005 ⁴⁴ England	1333 (0) [3.0–5.4 cm]	36/5465.3	12/3110.8 [3.0–5.4 cm] (fatal NR)	0.39 (0.20 to 0.67)	
Brown, 2003 ²⁹ Canada	895 (207) [3.0–4.9 cm]	0/3088	0/3088	0.00 (0.00 to 0.12)	1. Some patients also may be reported in study Brown 2003 ⁴³
Santilli, 2002 ³⁶ USA	790 (0) [3.0–3.9 cm]	0/3071.32	0/unknown	Unknown	1. Cause of death only available in 43% of patients, so some deaths from rupture may have been excluded 2. Only included patients with more than one scan
Reed, 1997 ⁴⁵ USA	176 (64–69) [<3 to >6 cm]	11/862	1/333 [3.0–5.0 cm] (fatal NR)	0.30 (0.01 to 1.67)	1. Rupture rates calculated from last US diameter 2. Only included patients with more than one scan
Guirgus, 1991 ⁴⁶ Canada	300 (89) [2.5–5.0 cm]	14/850	2/unknown (fatal NR)	Unknown	
Armstrong, 2007 ⁴⁷ USA	334 (3) [4.0–5.4 cm]	2/946	2/946 [4.0–5.4 cm] (1 fatal)	0.21 (0.03 to 0.76)	1. Surveillance group only

continued

TABLE 4 Studies reporting on the rupture rate of small AAAs (3.0–5.5cm in diameter) (*continued*)

Author, year and country	Total number of patients (women) [baseline AAA diameter]	Total ruptures per total person-years reported	Total small aneurysm ruptures per small aneurysm person-years [diameter range for subgroups] (fatal ruptures by 30 days)	Rate of small aneurysm ruptures per 100 person-years (95% CI)	Comments
Vega de Céniga, 2006 ³² Spain	352 (19) [3.0–5.0 cm]	2/1619	0/unknown	Unknown	1. Only includes patients with more than one scan
Propranolol Aneurysm Trial Investigators, 2002 ⁴⁰ Canada	552 (88) [3.0–5.0 cm]	At least 3/1380	At least 2/unknown (<5.5 cm fatal NR 2/3 total ruptures)	Unknown	1. Excluded patients whose AAA had grown by <2mm in previous year 2. No sudden deaths reported as rupture after mortality committee review
McCarthy, 2003 ³⁷ England	1423 (0) [2.5–4.0 cm]	2/5045	2/unknown (2 fatal)	Unknown	1. Unclear how many person-years are included beyond 5.5 cm
Lederle, 2002 ²² USA	567 (5) [4.0–5.4 cm] surveillance group only	11/1833	9/1833 [4.0–5.4 cm] (8 fatal)	0.49 (0.22 to 0.93)	1. Two covered 'hole in wall' at elective repair cases excluded: not true ruptures
Schlosser, 2008 ⁴¹ Netherlands	230 (23) [3.0–5.5 cm]	7/755	6/unknown (<5.5 cm fatal NR; 6/7 total ruptures)	Unknown	

NR, not reported.

For many studies the conditional follow-up for an aneurysm diameter of 3.0 to 5.5 cm, to aneurysm rupture or death could not be established.

TABLE 5 Further characteristics of included studies reporting on the rupture rate of small AAAs (3.0–5.5 cm in diameter)

Author, year and type of study (R, P, PR)	Inclusion criteria (aortic diameter ranges)	Age (years) of participants (mean)	Surveillance policy	Intervention policy ^a	Ascertainment of rupture described?	Time between last diameter and rupture reported?	Rupture rates as published
Brown and Powell, 1999 ²³ P	AAA >3 cm (3.0–3.9; 4.0–5.5; 5.6–9.7 cm)	70	US 4–4.9 cm: 6 months 5–5.5 cm: 3 months	> 5.5 cm	Yes	Yes	Annual rupture rate: 2.2% (95% CI 1.7% to 2.8%), large and small aneurysms
Buckingham <i>et al.</i> , 2007 ⁴² PR	AAA 3–5.5 cm; fit for surgery (2.8–7.8 cm)	73 (median)	US, varied with sex and size	Men > 5.5 cm Women > 5.0 cm	No	No	NR
Brown <i>et al.</i> , 2003 ⁴³ P	AAA 5–5.9 cm; unfit for surgery	73	US, 6-monthly	All patients unfit for surgery	No	No	1% per year (men); 3.9% per year (women); large and small aneurysms
Scott <i>et al.</i> , 2005 ⁴⁴ P	AAA 3–5.5 cm; men aged 65–74 years	NR	US 3–4.4 cm: yearly 4.5–5.4 cm: 3-monthly	5.5 cm	No	No	36 per 1000 person-years (95% CI 15 to 75 per 1000 person-years) for those with an AAA > 5.5 cm at recall
Brown <i>et al.</i> , 2003 ²⁹ P	AAA 3.0–5.0 cm	69	US, CT, 6-monthly	NR	No	NR	No ruptures
Santilli <i>et al.</i> , 2002 ³⁶ P	AAA 3–3.9 cm	69	US, variable	NR	No	NR	No ruptures
Reed <i>et al.</i> , 1997 ⁴⁵ P	AAA not for surgery (< 3 to > 8 cm)	74	US, NR	NR	Yes	Yes	By last diameter: 3–3.99 cm: 0 ruptures per PY; 4–4.99 cm: 0.007 ruptures per PY; 5–5.99 cm: 0.11 ruptures per PY

continued

TABLE 5 Further characteristics of included studies reporting on the rupture rate of small AAAs (3.0–5.5 cm in diameter) (continued)

Author, year and type of study (R, P, PR)	Inclusion criteria (aortic diameter ranges)	Age (years) of participants (mean)	Surveillance policy	Intervention policy ^a	Ascertainment of rupture described?	Time between last diameter and rupture reported?	Rupture rates as published
Guirgius and Barber, 1991 ⁴⁶ PR	AAA initially managed non-operatively (2.5–9.3 cm)	70	US, CT, 6-monthly	NR	No	No	NR
Armstrong <i>et al.</i> , 2007 ⁴⁷ PR	AAA 4–5.4 cm	NR	US, CT, MRI 3–4 cm: yearly 4–5.4 cm: biannually	> 5.4 cm	No	No	Cumulative incidence only reported
Vega de Céniga <i>et al.</i> , 2006 ³² P	AAA 3–4.9 cm	71	US: yearly if < 4 cm CT: every 6 months	> 5.0 cm	No	No	NR
Propranolol Aneurysm Trial Investigators, 2002 ⁴⁰ P	AAA 3–5.0 cm; no contraindications to propranolol	69	US, 6-monthly	Variable, > 4.5 cm or > 5.0 cm by centre	No	No	NR
McCarthy <i>et al.</i> , 2003 ³⁷ P	AAA 2.6–3.9 cm	65	US 2.6–3.9 cm: yearly 4.0 cm: 6-monthly	> 5.5 cm	No	Yes	2-year rupture rate: 1.4% (3.5–3.9-cm group), 0% at 3 years for smaller aortas

Author, year and type of study (R, P, PR)	Inclusion criteria (aortic diameter ranges)	Age (years) of participants (mean)	Surveillance policy	Intervention policy ^a	Ascertainment of rupture described?	Time between last diameter and rupture reported?	Rupture rates as published
Lederle <i>et al.</i> , 2002 ²² P	AAA 4–5.4 cm; randomised to surveillance	68	US, 6-monthly	> 5.4 cm	Yes	No	<0.6% per year of follow-up of unrepaired aneurysms
Schlosser <i>et al.</i> , 2008 ⁴¹ P	AAA 3–5.5 cm	66	US 3–3.9 cm: yearly 4–5.5 cm: 6-monthly	> 5.5 cm	No	No	0.9% per PY, including aneurysms > 5.5 cm

MRI, magnetic resonance imaging; NR, not relevant; P, prospective study; PR, prospective and retrospective contributions; R, retrospective study; PY, person-year.
^a Elective repair is contingent on patient fitness and consent; in addition, most studies reported being willing to repair the aneurysm for aneurysm-related symptoms and rapid growth (> 1 cm/year).

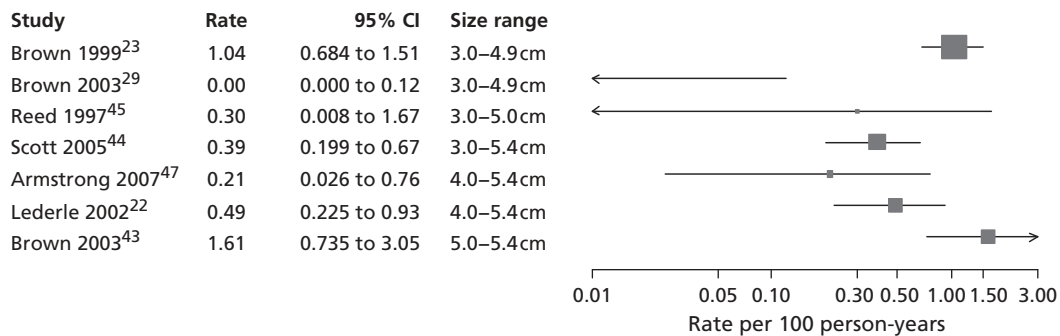


FIGURE 6 Rupture rates (per 100 person-years) for small AAAs in each study, reporting conditional follow-up to 5.5-cm threshold, sorted by reported size range (total 5934 patients). Aneurysms reaching >5.5cm have been excluded. These studies are depicted in order of increasing aneurysm size range, but the distribution of diameters within these size ranges is not available.

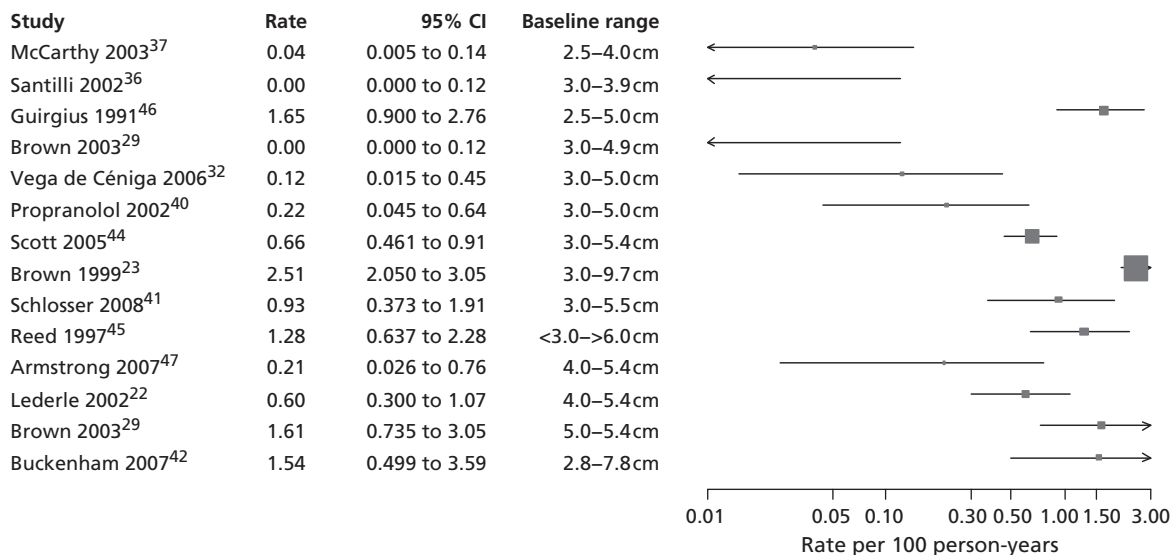


FIGURE 7 Total rupture rates (per 100 person-years) for small AAAs in each study, sorted by baseline diameter range (total 9779 patients). Including follow-up >5.5cm. These studies are depicted in order of increasing aneurysm baseline size range, but the distribution of diameters within these size ranges and over time is not available.

Chapter 5 Methods for individual patient data analysis of existing surveillance data

As revealed by the literature reviews (see *Chapters 3 and 4*), published data were insufficient for the detailed modelling of small AAA growth rates and rupture rates necessary to better inform surveillance intervals. Therefore, IPD were sought for this purpose. This chapter describes the methods used and *Chapter 6* provides the results.

In addition, surveillance intervals should be chosen to control to acceptable limits the risk of a small AAA reaching 5.5 cm, or of rupture, before the next scan. Such acceptable limits were informed by a focus group that we organised and which is also described in this chapter.

Data collection

Under the name of the RESCAN Collaboration, requests for IPD were addressed to the corresponding authors of 25 studies, each including more than 100 patients with small AAAs (3.0–5.5 cm in diameter) in a surveillance programme. Data sets for potential inclusion had been identified through a systematic literature search up to the end of 2009, as described in *Chapters 3 and 4*, and manual searching of abstracts from vascular surgical meetings during the interval 2007–10. Additional studies published up to September 2012 are discussed in *Chapter 9*.

The items requested included patient age, sex, sequential aneurysm diameters, ethnicity, smoking history, body mass index (BMI), presence of diabetes, dates of aneurysm repair, aneurysm rupture or death. The method used for US AAA diameter assessment was recorded for each study as internal (inner to inner luminal surface) or external (outer to outer aortic wall). A few studies used CT scans for some AAA measurements. Supplementary information for baseline histories of medication use, coronary and peripheral arterial disease as well as blood pressure was requested, if available. To allow for changing environmental factors (e.g. smoking), improvements in imaging quality as well as improving cardioprotective drug therapy, we also included year of patient enrolment as a variable. Additional information regarding AAA rupture (including death due to rupture), operative AAA repair and non-AAA death was collected for each patient where this was available. The definition of aneurysm rupture was pragmatic, based on locally used definition and reporting.

The RESCAN collaborators provided data for 18 studies, which were then subject to cleaning through an iterative process of correspondence with the study investigators to improve data quality, prior to the harmonisation of the data sets. All data sets were anonymised and, therefore, the study was subject to an ethical waiver.

For each individual, the baseline measurement was defined as the first measurement recorded between 3.0 and 5.4 cm. Measurements taken prior to a patient reaching a threshold of 3.0 cm were removed from the data sets. All data following baseline measurement were used until either a rupture event or censoring occurred. Censoring was defined as the first occurrence of: (1) a diameter measurement ≥ 5.5 cm (with this measurement included in the data set to properly account for informative dropout);¹⁷ (2) non-rupture-related death; (3) an elective AAA operation; or (4) the administrative censoring date of the data set. A patient's series of measurements was not censored if the aneurysm diameter dropped to < 3.0 cm, thus allowing some patients to have negative growth rates.

Focus group

In order to determine the level of risk of rupture or progression to 5.5 cm that would be acceptable to patients with small AAA, we conducted a patient focus group meeting. Men with small AAAs under surveillance in the Leicestershire AAA Surveillance Programme were invited to attend a meeting with a consultant vascular surgeon (MJ Bown) after verbal and written information about the RESCAN project was provided. A further explanation of the aims of the RESCAN project and its potential outcomes was given to the patients who attended the meeting prior to discussing the specific points below. Although the main aim of this focus group was to determine what risk of rupture and what risk of progression to a size threshold of 5.5 cm was acceptable to patients, a number of other issues relating to the surveillance of small AAA were discussed and these results are included below. The issues directly discussed were the acceptability of different intervals between surveillance scans, whether or not surveillance should be personalised, what factors patients think would improve surveillance, and what risks of rupture/progression were acceptable.

Surveillance intervals

The patients identified that the opinion of their surgeon was the most important factor that should influence the interval between surveillance scans. The patients expressed a wish to have surveillance intervals personalised depending on previous scan results and that any known factors influencing AAA growth should be taken into account when deciding surveillance intervals on an individual basis. The patients stated that sudden increases in AAA growth should mandate an expedited follow-up scan before their next scheduled scan and that AAA sizes of > 5 cm should also result in more frequent surveillance. The patients could not agree on a suitable time interval for such 'early recall' scans but felt that their surgeon should decide on the interval on an individual basis, taking absolute AAA size and rate of growth into account. The group stated that for the purposes of surveillance programmes (where vascular surgeons may not be directly involved in the decision-making process), the intervals between scans in the event of rapid growth should be standardised in a protocol to be followed by the surveillance programme.

Personalised surveillance

The group agreed that there was not enough evidence to base surveillance intervals on factors such as diabetes and smoking habits (summary data from a RESCAN publication⁴⁸ were presented to the group). It was noted that there were no smokers in the group. However, the patients felt that size should not be the only guiding factor in the timing of scans, and that other factors should also be considered if there proved to be good evidence for these factors in the future.

Improving surveillance

The focus group participants stated that too much information is given to them in verbal format at the time of surveillance scans. The group felt that a personal written record would be informative for some, even though it might not be practically useful to the patient directly. Participants agreed that they wish to know the AAA measurement at the time of the scan and, also, what the implications of that measurement are. The group felt that this information could be formulated into a booklet that could include their personal measurements.

Acceptable risks of reaching 5.5 cm between surveillance scans

In order to determine the acceptable risk of attaining an AAA measurement of 5.5 cm between surveillance scans, the patients were asked what chance of reaching a threshold size of 5.5 cm was acceptable. There was a mixed response from the group in response to this. All patients agreed that there was always some risk of reaching 5.5 cm at the time of his or her next scan. All present agreed that a risk of up to 10% was acceptable, with some stating that this chance could even be as high as 20%. The patients pointed out that reaching a size of 5.5 cm was the threshold for referral to a vascular surgeon for consideration of surgery rather than being a size where surgery had to be performed. The patients stated that if they were not aware of this then the acceptable risk of reaching 5.5 cm would be likely to be much lower. The group stated that the general public, uneducated about aneurysmal disease, may say that no risk is acceptable, regardless of cost.

Acceptable risks of abdominal aortic aneurysm rupture between surveillance scans

The risk of AAA rupture before the next surveillance scan was discussed. Some patients felt that some risk of rupture was unavoidable as they recognised that even small AAAs can rupture. This section of the group felt that the risk should be <2–3%. Some members of the group felt that there would be no point in participating in a surveillance programme unless the risk of rupture could be reduced to <1%. All present felt that a surveillance interval that resulted in a 5% risk of rupture by the time of their next scan would be unacceptable.

Conclusion

This patient focus group indicated that patient experiences of AAA surveillance are generally positive. Patient satisfaction may be improved through more use of written information or individual patient-held records, but this would need to be determined in a larger patient group before widespread adoption. All patients stated that a 10% risk of reaching an AAA size of 5.5 cm between surveillance scans, and a 1% risk of rupture between scans, were acceptable. These risk thresholds (10% risk of expansion to 5.5 cm and 1% risk of rupture) were therefore used in the analyses of the IPD data sets, as described below.

Statistical methods

Full details of the statistical methods are provided in *Appendix 3*. A summary is given here.

Growth rates

Each study was analysed separately. Linear random-effects models were used, since linear and quadratic models had previously been shown to provide similar predictions over the period required to assess AAA surveillance intervals.¹⁷ This method allows for individual variation in baseline diameters and growth rates, modelled as correlated random effects from a bivariate normal distribution, and independently normally distributed within-person variation (measurement error). Where both US and CT scans had been used to measure AAA diameter within the same study, an additive adjustment to the CT measurements was estimated within the analysis noting that scanning modality did not affect the estimated rate of growth.⁴⁸ Growth rates were estimated separately for men and women, through the inclusion of an interaction term. Results are primarily shown for men alone since this is the usual population of interest for AAA screening programmes.

Rupture rates

A joint model of AAA rupture and growth was employed.⁴⁹ The longitudinal AAA diameter measurements were fitted using a linear random-effects growth model as above, while a proportional hazards model with constant baseline hazard was used for the time-to-event rupture data. A log-linear effect of underlying diameter on risk of rupture was assumed. At least two ruptures per study were required to fit these models. An effect of sex on risk of rupture was included for studies that recruited both sexes.

Meta-analysis of growth and rupture rates

The following quantities were estimated from the growth and rupture models for each study: (1) mean growth rate given a baseline AAA diameter; (2) time taken to reach a 10% chance (as indicated by the focus group) of crossing the threshold for surgery (5.5 cm) given a baseline diameter; (3) the risk of rupture given underlying AAA diameter; and (4) the time taken to reach a 1% chance (as indicated by the focus group) of rupture given an underlying diameter. These outcomes were calculated for patients with an AAA between 3.0 and 5.4 cm, at 0.1 cm intervals, ignoring the risk of competing mortality from non-AAA causes of death. The estimates from each study were combined using random-effects meta-analysis,²⁵ and overall means, 95% CIs and 95% prediction intervals for each AAA diameter were calculated. Ninety-five per cent prediction intervals give the range of values between which values in a new study, similar to those in the data set, would be expected to lie.⁵⁰ Between-study heterogeneity was assessed using the I^2 measure,²⁶ which indicates the percentage of total variation across studies that is due to heterogeneity rather than chance.

Predictors of growth

Each predictor of growth was considered in a quadratic random-effects model through the inclusion of a main effect and an interaction term with the linear component of time, thus allowing an assessment of the effect on the growth rate. Indicator variables were used for binary covariates, whereas other covariates were considered as continuous variables. To allow studies that recorded both US and CT measurements to be included, a dummy variable was added to distinguish between the two modalities. The effect of modality on both the overall size and the growth rate was investigated. Both univariate and multivariate (adjusted) analyses were considered for each predictor variable. The multivariate model adjusted for baseline age, calendar year, sex, smoking, diabetes, mean arterial blood pressure/pulse pressure, history of cardiovascular disease, and additionally any recorded use of angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, statins or lipid-lowering drugs, and antiplatelet agents. The use of these drugs was generally recorded only at entry into each study. History of cardiovascular disease included angina, myocardial infarction, cardiac revascularisation, transient ischaemic attack, stroke and peripheral arterial disease. Studies that did not collect all these covariates were adjusted for as many covariates in the list as possible. Patients who had missing data on any of their study's covariates were excluded in the multivariate analyses.

Predictors of rupture

Cox regression models were used to assess the effect of each predictor variable on the risk of rupture in each study. All analyses were adjusted for AAA diameter, which was entered as a time-varying covariate. Owing to the small number of ruptures in each study, some covariate effects were not estimable.

Meta-analysis of effects of predictors

The parameter estimates and SEs were extracted from the above analyses for each study. Estimates for each predictor variable were pooled across all studies that provided an estimate, using random-effects meta-analysis as above.

Chapter 6 Results of individual patient data analysis of existing surveillance data

Study characteristics

Individual patient data were obtained from 18 different studies from Europe, Canada, the USA and Australia, with patients being admitted to these studies between 1983 and 2008; a summary of these studies is given in *Table 6*. A total of 15,475 patients are included, with an average of 4617 AAA measurements and 4.0 years of follow-up per study (*Table 7*). Not all patient demographics were available from all studies, and in some studies the data were incomplete for some individuals. Ethnicity was poorly reported. Baseline drug history was fully available in seven studies (see *Table 7*). Prevalence of drug use varied considerably between these studies (ACE inhibitors 9–41%, beta blockers 14–52%, calcium channel blockers 12–28%, statins/lipid-lowering drugs 0–78%, antiplatelet agents 27–94%). Data were not available from two randomised controlled trials (RCTs) and five other studies with a total of 2487 persons (see *Appendix 3*).

Study-specific thresholds for surgical intervention varied from 4.5 cm up to 6.0 cm (see *Table 6*). The majority of studies measured external (outer-to-outer) wall diameters, although three studies^{10,37,53} measured internal diameters. Rupture and censoring events were recorded in 14 out of the 18 studies allowing rupture rates to be investigated. The remaining four studies were used in the growth analysis only (see *Table 6*).

Four studies, Leeds (Professor D Julian A Scott, University of Leeds, 2010–12, personal communication), PIVOTAL,⁵¹ Galdakao³² and Stirling (Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication), measured diameters using both US and CT scans. CT measurements were on average significantly larger than US measurements [Leeds 3.91 mm (SE 0.33 mm), PIVOTAL 1.75 mm (SE 0.21 mm), Galdakao 1.77 mm (SE 0.10 mm), Stirling 2.46 mm (SE 0.27 mm)]. However, there was no evidence of an effect of modality on estimated growth rates (i.e. a CT measurement was found to be larger than an US measurement throughout follow-up by a constant amount). Therefore, within each study an additive adjustment could be applied so that all measurements were included in the analysis of growth rates.

Small abdominal aortic aneurysm growth rates in men

The overall pooled estimates of AAA growth in men increased by about 0.5 mm/year for each 0.5-cm increase in baseline AAA diameter (*Figures 8 and 9*). The average estimated growth rate in men was 1.3 mm/year (95% CI 1.0 mm/year to 1.5 mm/year) for a 3.0-cm aneurysm and 3.6 mm/year (95% CI 3.3 mm/year to 3.9 mm/year) for a 5.0-cm aneurysm (*Table 8*). However, there was also substantial heterogeneity in growth rates between studies, so the 95% prediction intervals were wide. Much of this heterogeneity is unexplained. Although smokers and non-diabetics have higher rates of growth (see *Predictors of abdominal aortic aneurysm growth rates*), these factors did not explain the heterogeneity between studies: adjusting for baseline AAA diameter, smoking and diabetes only reduced the overall percentage of variation due to heterogeneity from 97.5% to 94.1%. Excluding the three studies (Chichester,⁵³ Gloucestershire³⁷ and MASS¹⁰) that measured internal diameters, the pooled mean growth rates decreased by between 0.10 mm/year and 0.13 mm/year, depending on baseline diameter, but the percentage of variation due to heterogeneity only decreased by between 1.5% and 3.3%.

TABLE 6 Summary of IPD sets for IPD meta-analysis

Study (reference)	Mean calendar year at baseline	Threshold for intervention (cm)	Measurement modalities used	Internal/external diameter measured	Number of men/women	Mean follow-up (years) for men/women	Number of small AAA ruptures in men/women	Crude rupture rate (per 1000 person-years) in men/women
Western Australia ⁵²	1997	5.0 or 5.5 by centre	US only	External	685/0	8.24/NA	4/NA	0.71/NA
^a Bournemouth, UK	2002	5.5	US only	External	677/0	3.44/NA	NA/NA	NA/NA
Chichester, UK ⁵³	1999	6.0, later 5.5	US only	Internal	1405/99	4.45/4.42	43/8	6.88/18.26
Edinburgh, UK ⁵⁴	NA ^b	5.5	US only	External	670/382	2.89/2.42	NA/NA	NA/NA
Gloucestershire, UK ³⁷	2000	5.5	US only	Internal	1981/0	4.70/NA	34/NA	3.65/NA
Huntingdon, UK ³⁴	1995	4.5	US only	External	629/0	3.87/NA	2/NA	0.82/NA
^c Leeds, UK	2004	5.5	US and CT	External	220/47	3.27/3.14	NA/NA	NA/NA
^d Leicester, UK	2002	5.5	US only	External	899/0	3.28/NA	NA/NA	NA/NA
^e Manchester, UK	2005	5.5	US only	External	837/258	2.41/2.41	6/5	2.97/8.03
MASS, UK ¹⁰	1998	5.5	US only	Internal	1122/0	5.42/NA	33/NA	5.42/NA
Tromsø, Norway ³⁸	1995	5.5	US only	External	179/45	8.59/8.16	2/2	1.30/5.45
PIVOTAL, USA ⁵¹	2007	5.0	US and CT	External	619/96	0.92/0.96	0/1	0.00/10.84
Propranolol, Canada ⁴⁰	1996	5.0 or 5.5 by centre	US only	External	460/88	2.47/2.39	3/0	2.64/0.00
Galdakao, Spain ³²	2001	5.0	US and CT	External	859/64	3.93/2.55	5/1	1.47/6.14
^f Stirling, UK	2003	5.5	US and CT	No set protocol	331/125	3.08/3.34	4/5	3.92/11.98
Gävle, Sweden ³⁹	2003	5.0 or 5.5 by centre	US only	External	184/59	2.46/2.52	1/0	2.21/0.00
UKSAT, UK ¹³	1993	5.5	US only	External	1747/480	2.38/2.65	32/28	7.68/22.00
Viborg, Denmark ⁵⁵	1996	5.0	US only	External	224/0	6.09/NA	9/NA	6.59/NA

NA, not available; UKSAT, United Kingdom Small Aneurysm Trial.

^a Mr Simon Parvin, Royal Bournemouth Hospital, 2010–12, personal communication.

^b Edinburgh study provided data at 6-month intervals only with no exact dates.

^c Professor D Julian A Scott, University of Leeds, 2010–12, personal communication.

^d Mr Matthew J Bown, University of Leicester and the NIHR Leicester Cardiovascular Biomedical Research Unit, 2010–12, personal communication.

^e Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication.

^f Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication.

TABLE 7 Summary of IPD provided from each study

Study (reference)	Number of patients (diameter measures)	Mean age at baseline (years)	% male (% missing)	% current smokers (% missing)	Mean BMI (kg/m ²) (% missing)	% diabetes (% missing)	Mean arterial blood pressure (mmHg) (% missing)	% history of cardiovascular disease (% missing)	Baseline drug history available
Western Australia ⁵²	685 (3738)	73.4	100.0 (0.0)	18.4 (0.7)	27.2 (0.7)	10.6 (0.7)	112.9 (0.7)	49.9 (9.3)	Yes
^a Bournemouth, UK	677 (2959)	72.8	100.0 (0.0)	NA	NA	NA	NA	NA	No
Chichester, UK ⁵³	1504 (9649)	69.6	93.4 (0.0)	NA	NA	NA	106.1 (18.9)	NA	No
Edinburgh, UK ⁵⁴	1052 (5155)	71.4	63.7 (0.0)	NA	NA	NA	NA	NA	No
Gloucestershire, UK ³⁷	1981 (12,442)	66.9	100.0 (0.0)	NA	NA	NA	NA	NA	No
Huntingdon, UK ³⁴	629 (3781)	70.1	100.0 (0.0)	29.8 (34.8)	NA	9.4 (54.4)	111.8 (7.0)	NA	Incomplete
^b Leeds, UK	267 (1870)	71.8	82.5 (0.0)	24.8 (0.7)	NA	15.4 (0.4)	107.4 (0.0)	54.9 (0.7)	Yes
^c Leicester, UK	899 (4689)	66.8	100.0 (0.0)	41.4 (1.9)	NA	NA	NA	28.3 (0.0)	No
^d Manchester, UK	1095 (5315)	74.0	76.4 (0.0)	NA	NA	NA	NA	NA	No
MASS, UK ¹⁰	1122 (8361)	70.2	100.0 (0.0)	31.8 (14.8)	NA	NA	106.9 (5.5)	NA	No
Tromsø, Norway ³⁸	224 (3817)	67.0	79.9 (0.0)	53.4 (0.4)	26.7 (0.0)	4.9 (0.0)	107.5 (0.0)	39.3 (0.0)	No
PIVOTAL, USA ⁵¹	715 (1753)	70.9	86.6 (0.0)	27.5 (2.0)	NA	20.7 (0.8)	NA	72.3 (2.9)	Yes
Propranolol, Canada ⁴⁰	548 (2971)	68.9	83.9 (0.0)	36.7 (0.0)	26.9 (0.2)	6.2 (0.0)	101.7 (0.0)	36.7 (0.0)	Yes
Galdakao, Spain ³²	926 (3466)	71.6	93.1 (0.4)	29.3 (0.0)	NA	15.7 (0.0)	NA	67.3 (0.1)	Incomplete
^e Stirling, UK	457 (1979)	71.7	72.6 (0.2)	NA	NA	NA	NA	NA	No
Gävle, Sweden ³⁹	243 (1114)	70.5	75.7 (0.0)	39.1 (0.0)	NA	4.1 (0.4)	NA	51.9 (0.0)	Yes
UKSAT, UK ¹³	2227 (9140)	69.4	78.4 (0.0)	38.0 (3.0)	25.0 (5.2)	4.3 (3.3)	109.7 (4.0)	26.7 (10.8)	Yes
Viborg, Denmark ⁵⁵	224 (912)	68.1	100.0 (0.0)	59.9 (14.3)	26.6 (13.8)	2.7 (0.0)	NA	36.6 (0.0)	Yes

NA, not available; UKSAT, United Kingdom Small Aneurysm Trial.

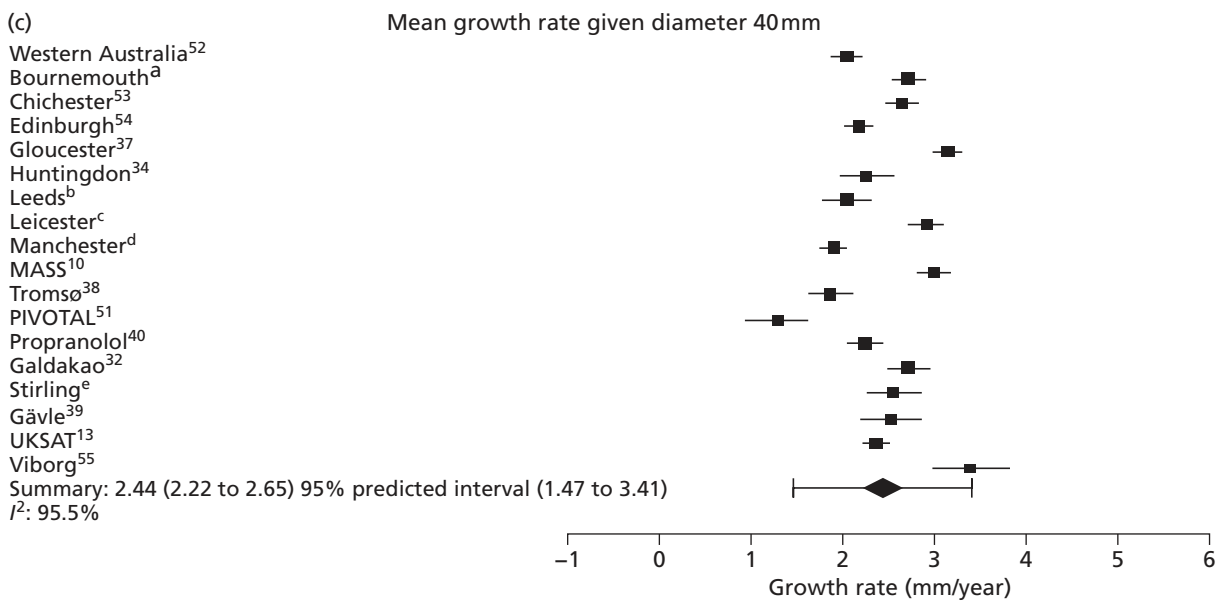
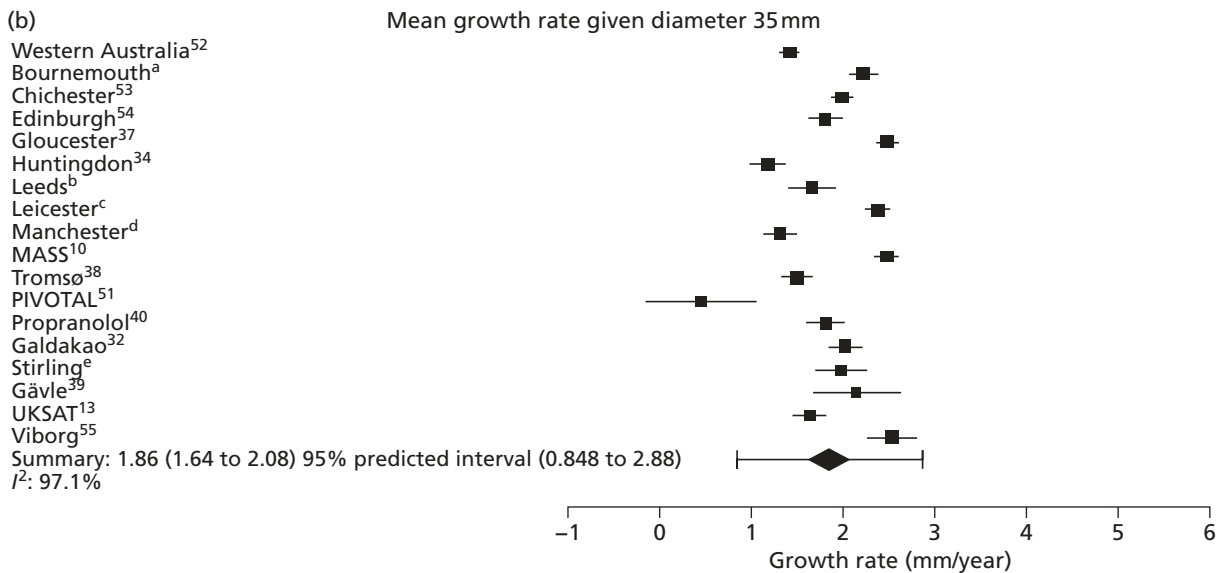
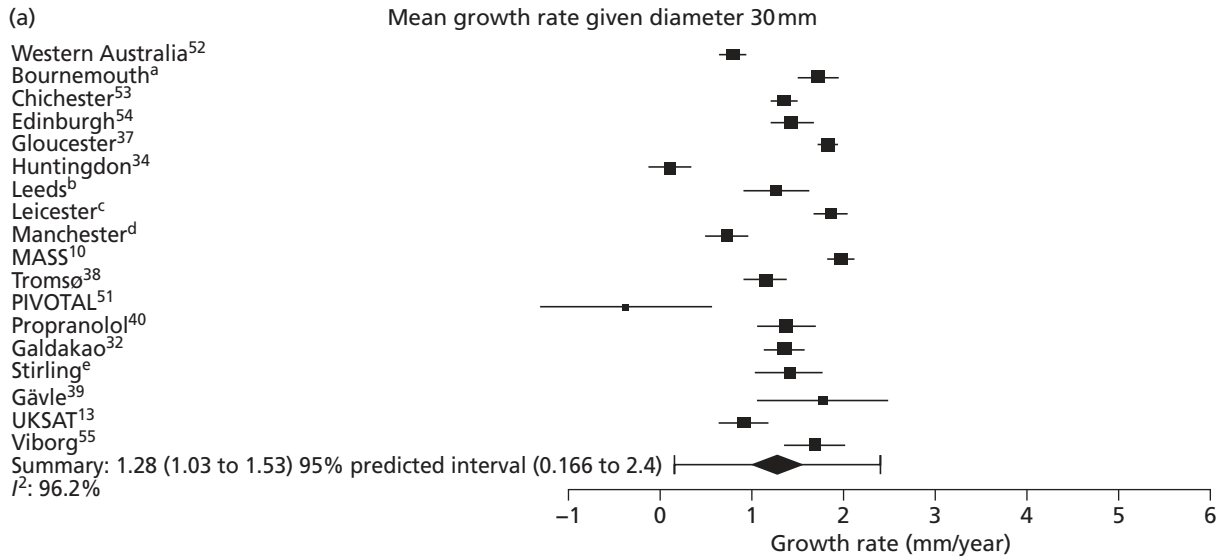
^a Mr Simon Parvin, Royal Bournemouth Hospital, 2010–12, personal communication.

^b Professor D Julian A Scott, University of Leeds, 2010–12, personal communication.

^c Mr Matthew J Bown, University of Leicester and the NIHR Leicester Cardiovascular Biomedical Research Unit, 2010–12, personal communication.

^d Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication.

^e Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication.



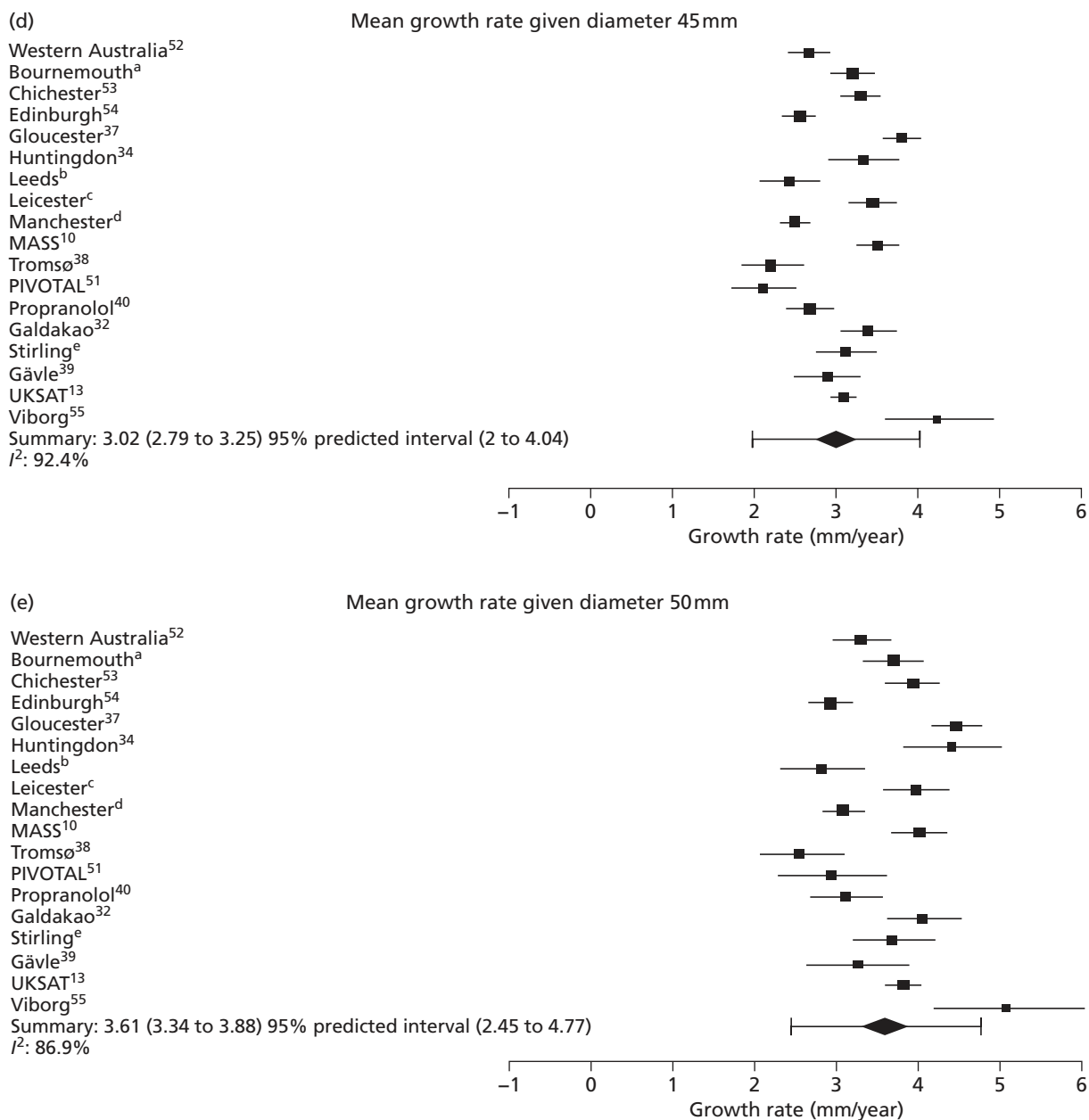


FIGURE 8 Forest plots of mean AAA growth rate (estimate and 95% CI) in men according to baseline AAA diameter. (a) Mr Simon Parvin, Royal Bournemouth Hospital, 2010–12, personal communication; (b) Professor D Julian A Scott, University of Leeds, 2010–12, personal communication; (c) Mr Matthew J Bown, University of Leicester and the NIHR Cardiovascular Biomedical Research Unit, 2010–12, personal communication; (d) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (e) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

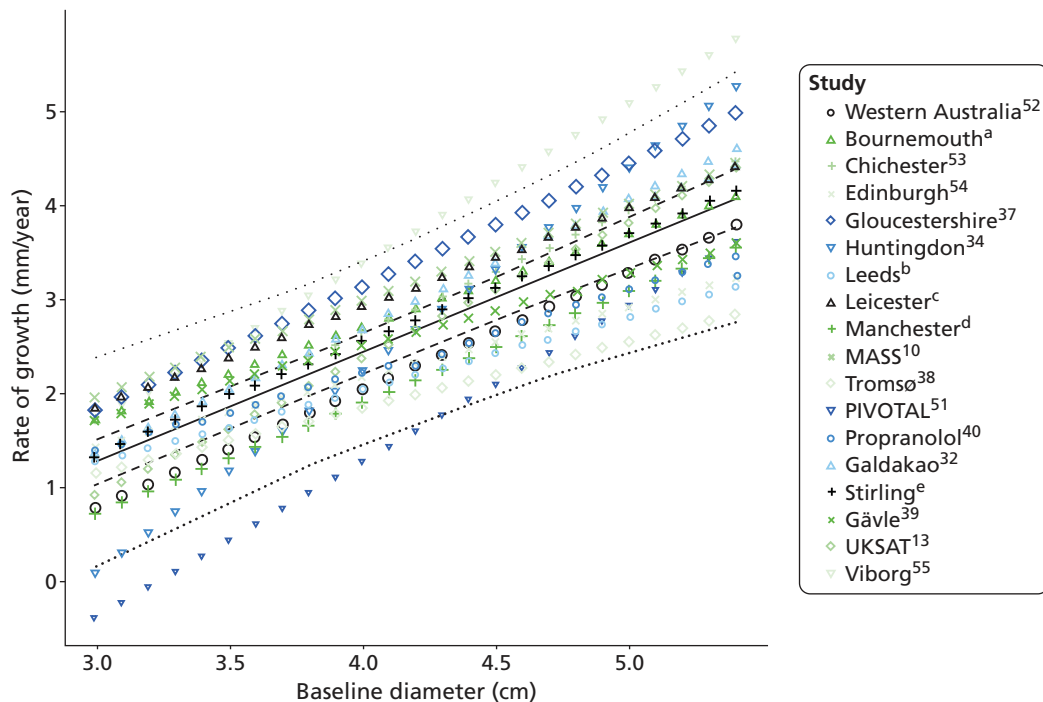


FIGURE 9 Estimated mean growth rate given baseline AAA diameter, in men, by study and overall (with 95% CIs and prediction intervals). The area of each symbol is inversely proportional to its SE. (a) Mr Simon Parvin, Royal Bournemouth Hospital, 2010–12, personal communication; (b) Professor D Julian A Scott, University of Leeds, 2010–12, personal communication; (c) Mr Matthew J Bown, University of Leicester and the NIHR Cardiovascular Biomedical Research Unit, 2010–12, personal communication; (d) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (e) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

TABLE 8 Pooled (meta-analysis) estimates of AAA growth and rupture for men and women separately, with 95% CIs (round brackets) and 95% prediction intervals [square brackets]

Meta-analysis estimate of:	Sex	AAA diameter (cm)				
		3.0	3.5	4.0	4.5	5.0
Growth rate (mm/year)	Men	1.28 (1.03 to 1.53) [0.17 to 2.40]	1.86 (1.64 to 2.08) [0.85 to 2.88]	2.44 (2.22 to 2.65) [1.47 to 3.41]	3.02 (2.79 to 3.25) [2.00 to 4.04]	3.61 (3.34 to 3.88) [2.45 to 4.77]
	Women	1.46 (1.07 to 1.85) [0.03 to 2.89]	1.98 (1.65 to 2.32) [0.75 to 3.22]	2.51 (2.22 to 2.81) [1.47 to 3.56]	3.06 (2.80 to 3.33) [2.18 to 3.95]	3.62 (3.36 to 3.89) [2.79 to 4.45]
Time taken to reach a 10% chance that the threshold for surgery has been crossed (years)	Men	7.4 (6.7 to 8.1) [4.9 to 11.3]	5.0 (4.6 to 5.4) [3.4 to 7.1]	3.2 (3.0 to 3.4) [2.3 to 4.4]	1.8 (1.7 to 2.0) [1.3 to 2.5]	0.7 (0.6 to 0.8) [0.4 to 1.2]
	Women	6.9 (6.1 to 7.8) [4.5 to 10.6]	4.8 (4.3 to 5.3) [3.3 to 6.8]	3.1 (2.9 to 3.4) [2.3 to 4.3]	1.8 (1.7 to 2.0) [1.3 to 2.5]	0.7 (0.6 to 0.8) [0.4 to 1.3]
Rate of rupture (per 1000 person-years)	Men	0.5 (0.3 to 0.7) [0.3 to 0.7]	0.9 (0.6 to 1.3) [0.5 to 1.5]	1.7 (1.1 to 2.4) [0.6 to 4.3]	3.2 (2.2 to 4.6) [1.0 to 10.0]	6.4 (4.3 to 9.5) [1.7 to 23.5]
	Women	2.2 (1.3 to 4.0) [0.9 to 5.7]	4.5 (2.8 to 7.2) [2.1 to 9.7]	7.9 (4.5 to 13.9) [1.7 to 36.1]	14.7 (8.1 to 27.7) [2.3 to 95.1]	29.7 (15.9 to 55.4) [3.9 to 222.9]
Time taken to reach a 1% chance of rupture (years)	Men	8.5 (7.0 to 10.5) [5.1 to 14.2]	5.5 (4.4 to 6.8) [2.8 to 10.7]	3.5 (2.8 to 4.3) [1.8 to 6.9]	2.2 (1.8 to 2.8) [1.1 to 4.4]	1.4 (1.2 to 1.8) [0.7 to 2.8]
	Women	3.5 (1.9 to 6.4) [0.8 to 14.6]	2.1 (1.2 to 3.6) [0.4 to 11.1]	1.4 (0.9 to 2.1) [0.3 to 5.8]	0.9 (0.6 to 1.4) [0.2 to 3.5]	0.7 (0.5 to 1.1) [0.2 to 3.3]

The length of time taken for men under surveillance to have a 10% chance of reaching the threshold size of 5.5 cm decreased substantially with baseline AAA diameter (Figure 10). For men with a 3.0-cm aneurysm, the estimated mean time taken to have a 10% chance of reaching 5.5 cm was 7.4 years (95% CI 6.7 years to 8.1 years). The corresponding mean times for 4.0-cm and 5.0-cm aneurysms were 3.2 years (95% CI 3.0 years to 3.4 years) and 0.7 years (95% CI 0.6 years to 0.8 years), respectively (see Table 8). Again, the prediction intervals were substantially wider than the CIs because of the heterogeneity between studies.

Small abdominal aortic aneurysm rupture rates in men

Overall the number of ruptures was small, with 178 reported events among 11,262 men under surveillance and 50 among 1314 women. Crude rupture rates in men in each study varied between 0 and 0.77 ruptures per 100 person-years (see Table 6). There were 12 studies with at least two ruptures available to assess the relationship between rupture rates and AAA diameter in men, and five studies in women (see Table 6). Rupture rates in men increased with baseline AAA diameter, approximately doubling for every 0.5-cm increase (Figures 11 and 12). The average rupture rates were 0.05 per 100 person-years (95% CI 0.03 to 0.07 per 100 person-years) for a 3.0-cm AAA and 0.64 (95% CI 0.43 to 0.95 per 100 person-years) for a 5.0-cm AAA. The degree of heterogeneity between studies also increased with baseline AAA diameter; I^2 ranged from 0% to 82% for diameters 3.0–5.4 cm. It was not possible to investigate the cause of this heterogeneity, due primarily to the small number of ruptures observed in each study making multivariate modelling infeasible. The time taken for men under surveillance to reach a rupture risk of 1% decreased with baseline AAA diameter (Figure 13). For AAA diameters in the range 3.0–4.5 cm the average time to reach a rupture risk of 1% was more than 2 years (see Table 8). For a 5.0-cm AAA, a 1% risk of rupture was reached on average in 1.4 years (95% CI 1.2 years to 1.8 years).

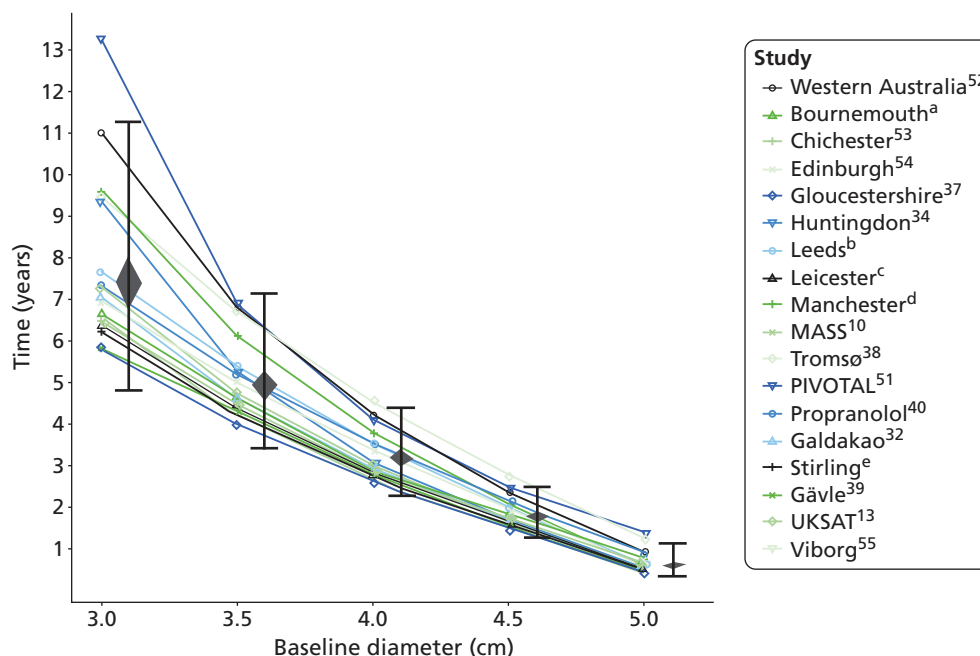


FIGURE 10 Estimated time given baseline AAA diameter for which there is a 10% chance that the threshold diameter for surgery (5.5 cm) has been reached, in men, by study and overall (black diamonds represent 95% CIs, error bars are 95% prediction intervals). (a) Mr Simon Parvin, Royal Bournemouth Hospital, 2010–12, personal communication; (b) Professor D Julian A Scott, University of Leeds, 2010–12, personal communication; (c) Mr Matthew J Bown, University of Leicester and the NIHR Cardiovascular Biomedical Research Unit, 2010–12, personal communication; (d) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (e) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

Small abdominal aortic aneurysm growth and rupture rates in women

The dependence of growth and rupture rates on AAA diameter was very similar in women and men (Figures 14 and 15 compared with Figures 8 and 11). Heterogeneity between studies was slightly less for women. Although absolute growth rates were similar for women and men (particularly for larger baseline AAA diameters), there were marked differences in the absolute risks of rupture. Women had about a fourfold greater rupture risk for all AAA sizes (see *Predictors of abdominal aortic aneurysm growth rates*), and reached a rupture risk of > 1% in a much shorter time than men (see Table 8).

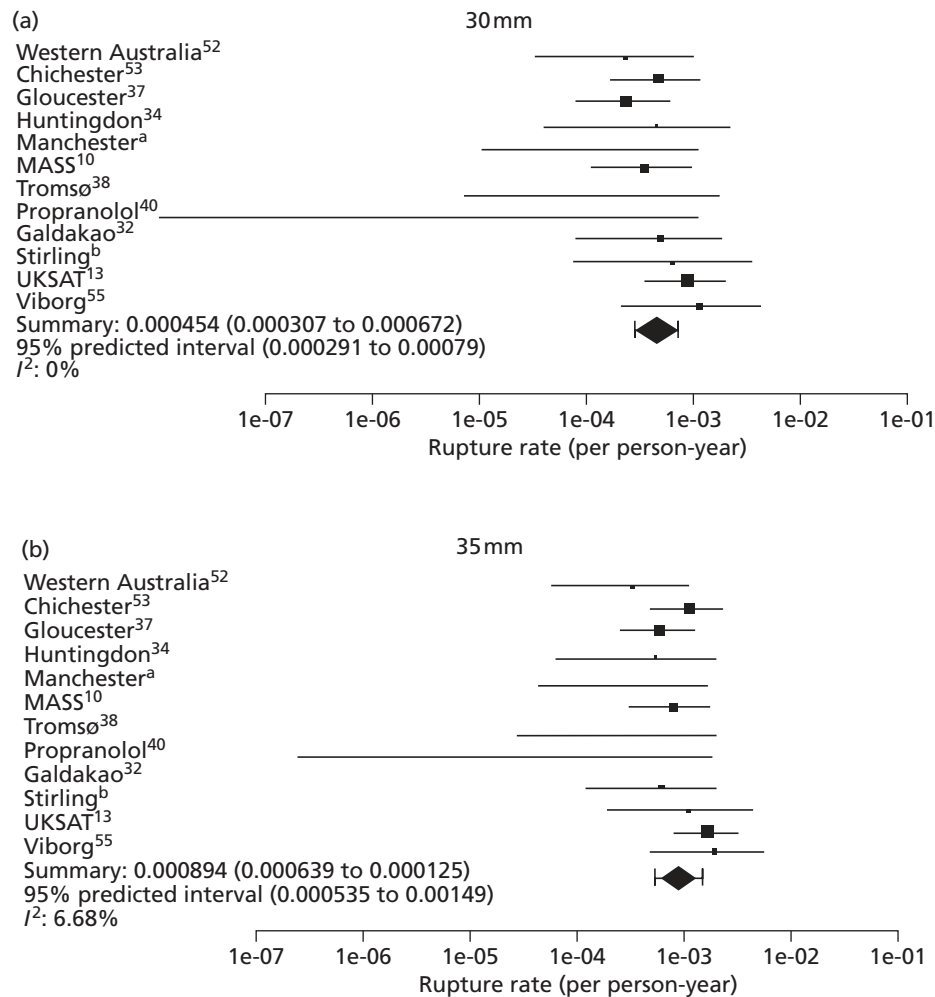


FIGURE 11 Forest plots of rupture risk (estimate and 95% CI, log-scale) in men according to underlying AAA diameter. (a) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (b) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial. (*continued*)

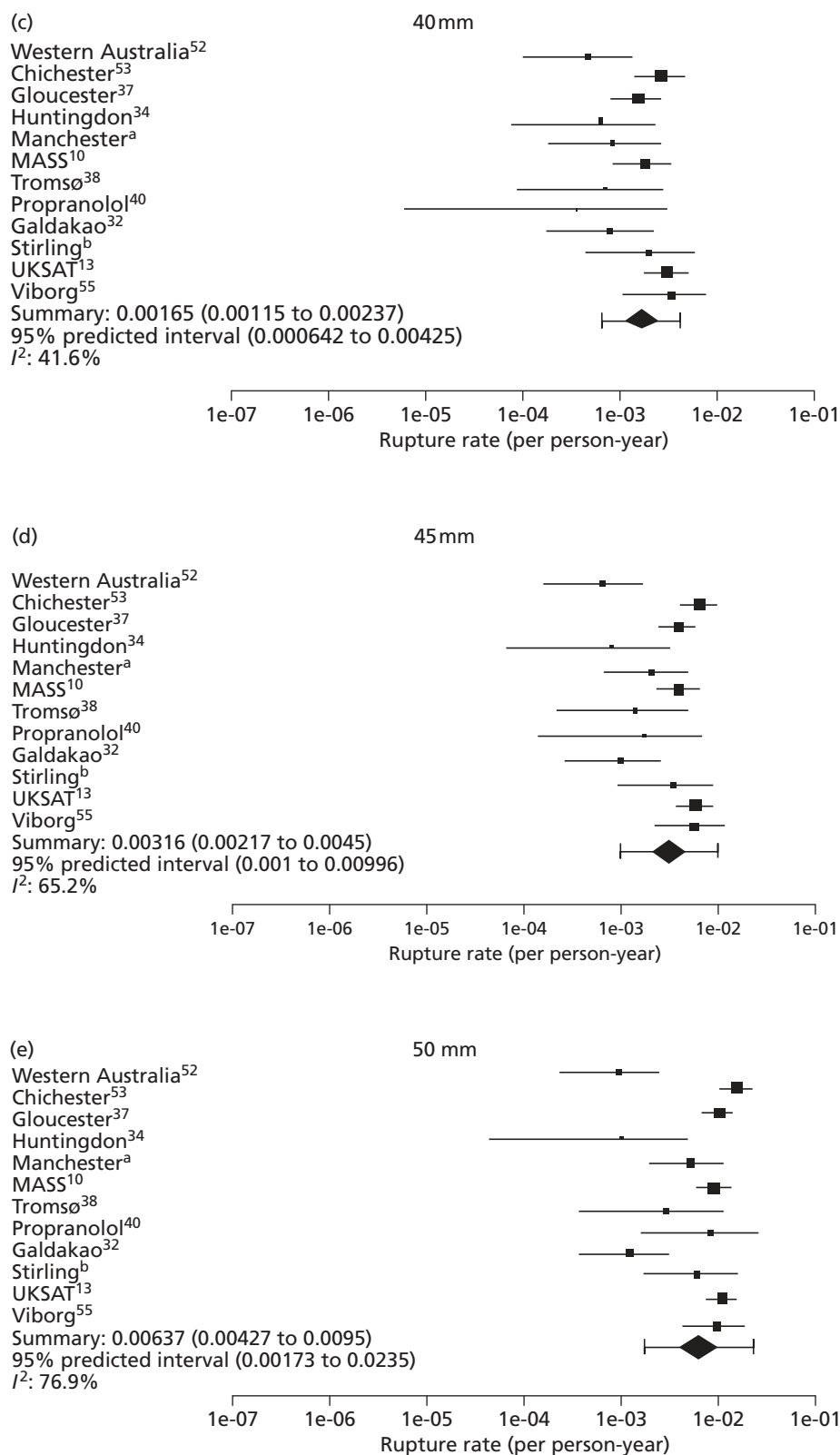


FIGURE 11 Forest plots of rupture risk (estimate and 95% CI, log-scale) in men according to underlying AAA diameter. (a) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (b) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

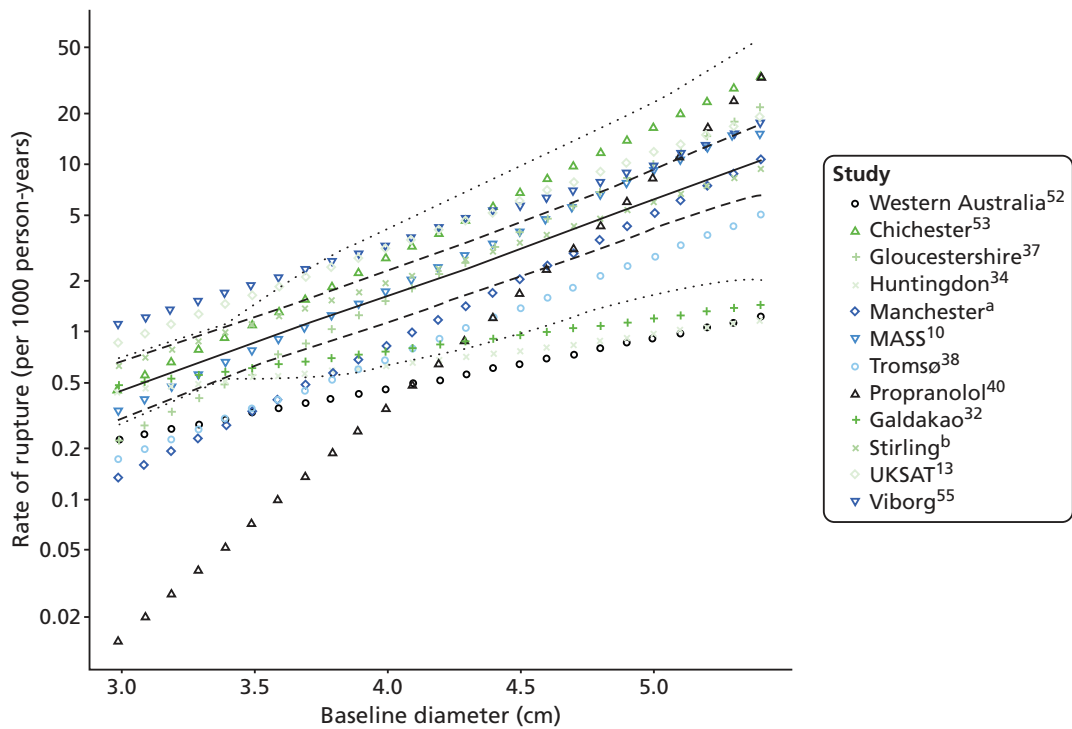


FIGURE 12 Rupture risk according to underlying AAA diameter, in men, by study and overall (log-scale, with 95% CIs and prediction intervals). The area of each symbol is inversely proportional to its SE. (a) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (b) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

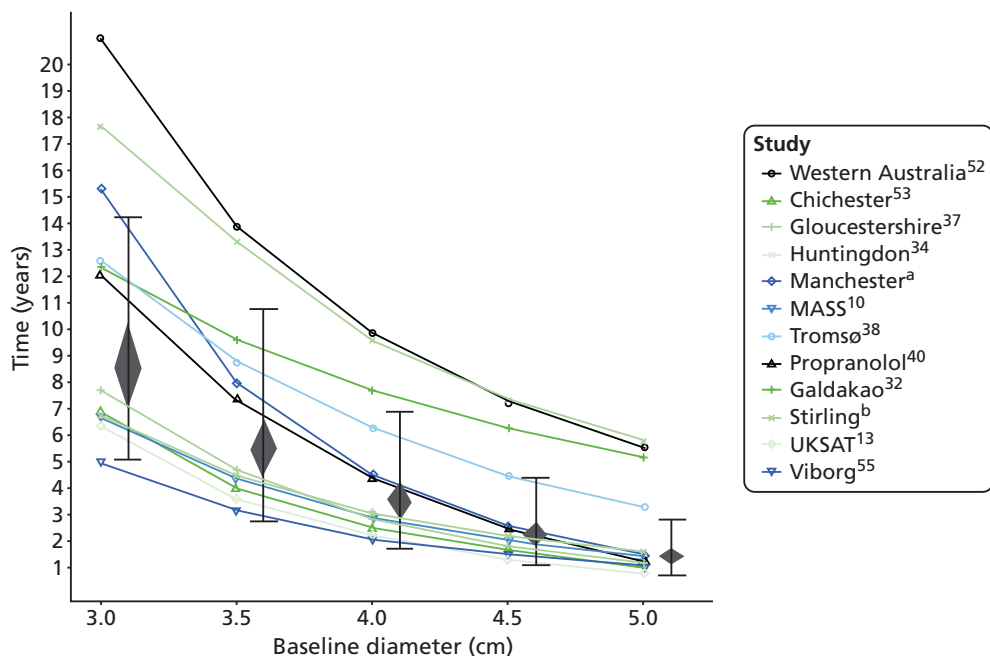


FIGURE 13 Estimated time given underlying AAA diameter for which there is a 1% chance of rupture, in men, by study and overall (black diamonds represent 95% CIs, error bars are 95% prediction intervals). (a) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (b) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

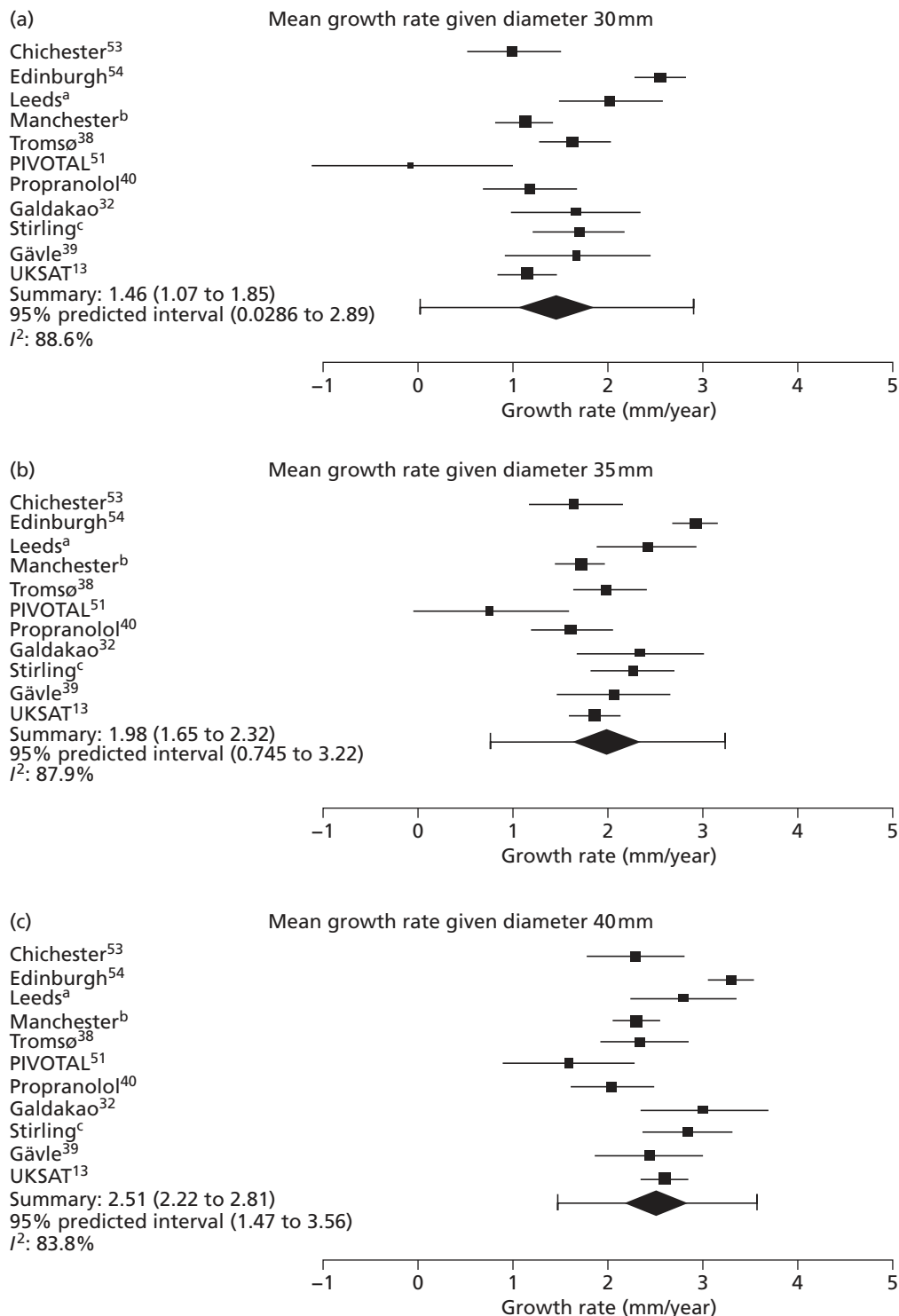


FIGURE 14 Forest plots of mean AAA growth rate (estimate and 95% CIs) in women according to baseline AAA diameter. (a) Professor D Julian A Scott, University of Leeds, 2010–12, personal communication; (b) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (c) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial. (*continued*)

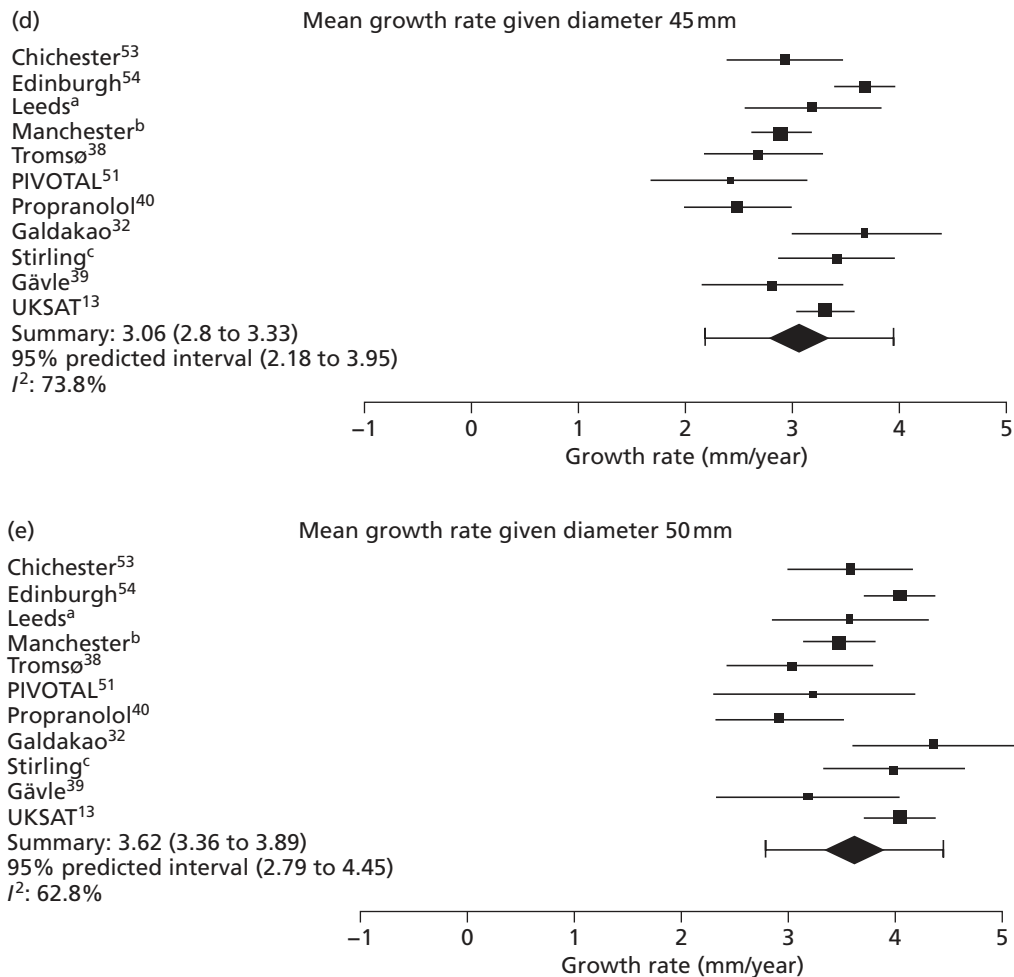


FIGURE 14 Forest plots of mean AAA growth rate (estimate and 95% CIs) in women according to baseline AAA diameter. (a) Professor D Julian A Scott, University of Leeds, 2010–12, personal communication; (b) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (c) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

Predictors of small abdominal aortic aneurysm growth rates

Unadjusted analysis of each demographic variable on aneurysm growth revealed significant effects among a number of individual study estimates. However, there was considerable heterogeneity between study estimates for many of the demographics considered (as measured using I^2). When estimates were pooled using random-effects meta-analysis (with adjustment for initial aneurysm diameter), current smoking was significantly associated with faster aneurysm growth rates, whereas increased BMI, diabetes, increased pulse pressure, and history of cardiovascular disease were associated with slower growth rates (*Table 9*). After adjustment for all demographics, medical history and drug history, only current smoking and diabetes remained significant predictors of aneurysm growth (see *Table 9*). The growth rate in current smokers was on average 0.35 mm/year (SE 0.07 mm/year; $p < 0.001$) faster than in ex or never smokers, whereas diabetics had growth rates that were on average 0.51 mm/year (SE 0.10 mm/year; $p < 0.001$) slower than non-diabetics. This evidence is consistent across the studies as demonstrated in *Figure 16*. Men and women had similar growth rates.

Associations between baseline use of cardiovascular drugs and aneurysm growth rate are shown in *Table 10*. Univariate analyses suggest that many of the drugs could be protective against aneurysm growth, with the largest effect coming from the use of statins/lipid-lowering drugs. However, the magnitude of these effects was relatively small and could be confounded with their prescription in specific risk populations.

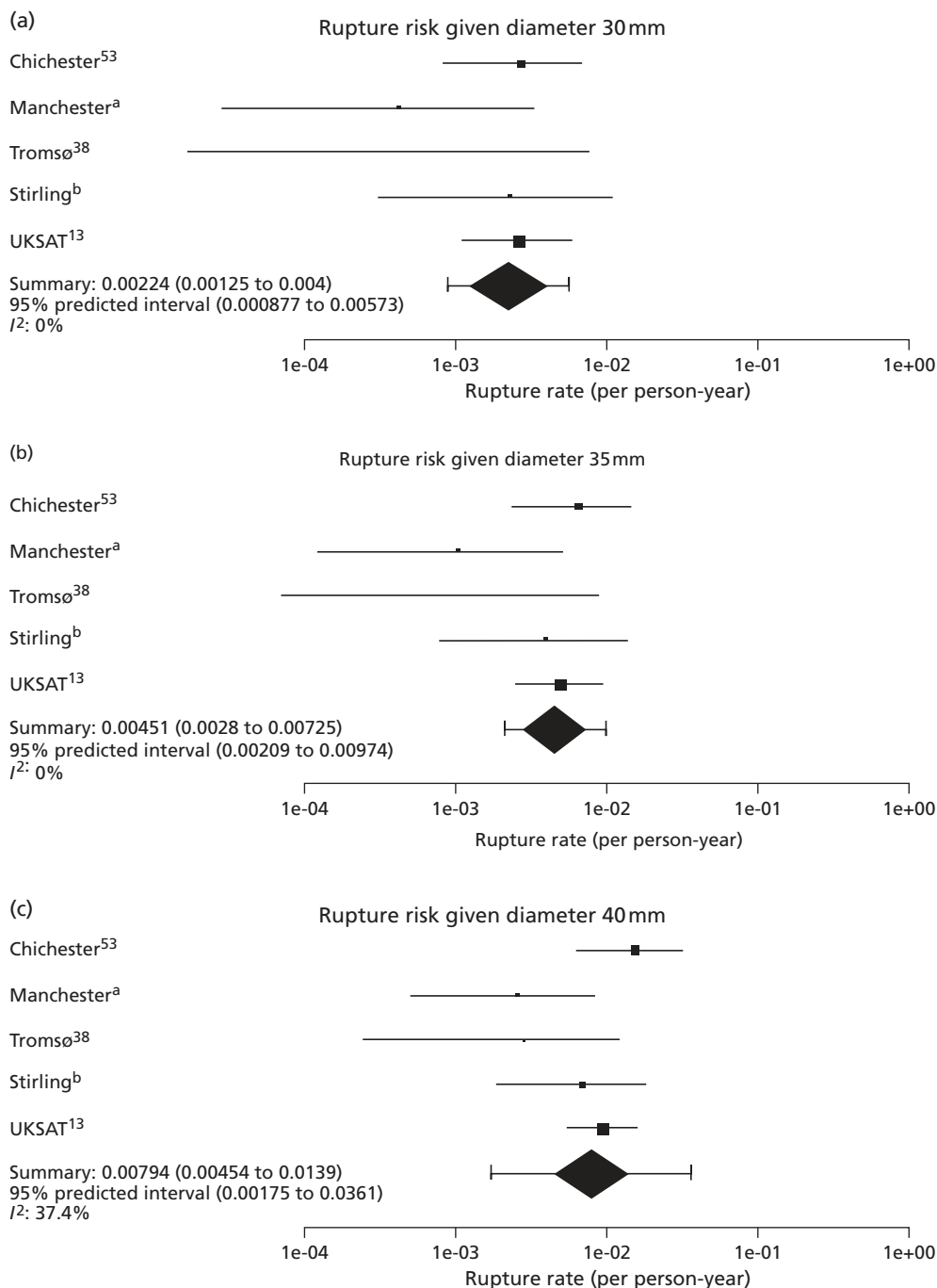


FIGURE 15 Forest plots of rupture risk (estimate and 95% CIs, log-scale) in women according to underlying AAA diameter. (a) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (b) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial. (*continued*)

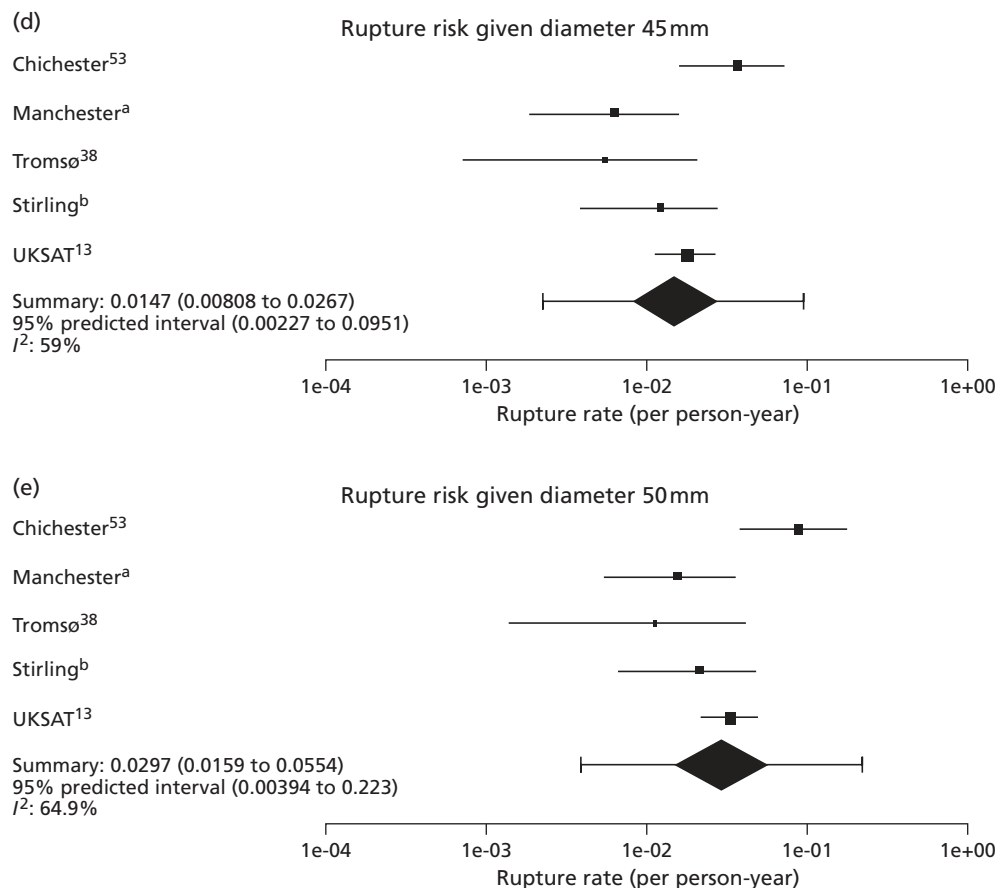


FIGURE 15 Forest plots of rupture risk (estimate and 95% CIs, log-scale) in women according to underlying AAA diameter. (a) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (b) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

Indeed, after adjustment for other demographics, the pooled meta-analysis estimates were no longer statistically significant for any class of drug investigated (see *Table 10*). Although the use of many of these drugs increased over time, calendar year of enrolment did not appear to influence aneurysm growth rate.

Predictors of small abdominal aortic aneurysm rupture rates

The differences in the crude rupture rates between the studies were large (from 0.07 up to 1.1 per 100 person-years). However, some of these differences could be explained by different baseline diameter ranges, different lengths of follow-up after last diameter measurement and proportions of women in each study. After adjustment for aneurysm diameter, the influence of demographics and medical history on rupture rates revealed a strong association between smoking and rupture [pooled hazard ratio (HR) 2.02, 95% CI 1.33 to 3.06; $p = 0.001$], and a far higher risk of rupture for women than men (pooled HR 3.76, 95% CI 2.58 to 5.47; $p < 0.001$) (*Figure 17*). The risk of rupture was also found to increase significantly for older patients, patients enrolled earlier in calendar time, those with lower BMI, and with higher mean arterial blood pressure or pulse pressure (*Table 11*). It was not possible to conduct fully adjusted analyses of these effects because of the small number of ruptures observed. However, effects did remain consistent after adjustment for age and calendar time.

Any association between cardiovascular drugs and aneurysm rupture was difficult to investigate with the present data because of the low prevalence of rupture and insufficient reporting of the drugs. Only six

TABLE 9 Meta-analysis of the influence of patient characteristics on small aneurysm growth rates

Characteristic	Number of studies	Unadjusted analyses				Adjusted analyses			
		Total number of patients	Estimate (SE) mm/year	p-value	I ² (%)	Total number of patients	Estimate (SE) mm/year	p-value	I ² (%)
Age at baseline (per year)	18	15,482	-0.004 (0.007)	0.559	76	13,966	-0.001 (0.006)	0.820	66
Calendar year at baseline (per year)	17	14,432	0.001 (0.021)	0.965	86	12,914	0.012 (0.022)	0.590	85
Sex (female vs. male)	11	9262	0.156 (0.144)	0.278	78	8472	0.142 (0.150)	0.344	78
Smoking (current vs. ex/never)	12	8196	0.375 (0.081)	<0.001	57	7486	0.354 (0.065)	<0.001	24
BMI (per kg/m ²)	5	3756	-0.017 (0.008)	0.039	0	3439	-0.008 (0.009)	0.348	0
Diabetes	10	6268	-0.596 (0.092)	<0.001	0	5697	-0.505 (0.097)	<0.001	0
Mean arterial blood pressure (per 10mmHg)	8	6723	0.003 (0.024)	0.886	74	5957	0.013 (0.021)	0.531	62
Pulse pressure (per 10mmHg)	8	6723	-0.040 (0.018)	0.024	67	5957	-0.027 (0.014)	0.060	46
History of cardiovascular disease	10	6638	-0.177 (0.075)	0.017	38	6302	-0.105 (0.088)	0.230	46

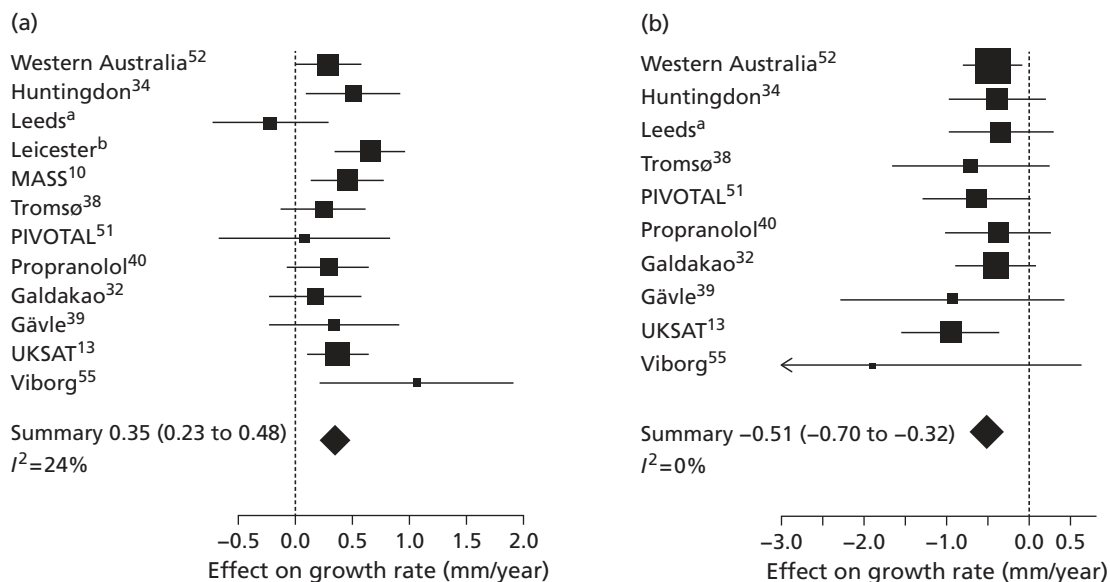
**FIGURE 16** Effect of (a) smoking status (current vs. ex/never) and (b) diabetes on aneurysm growth rates (mm/year) in individual studies and meta-analysis: adjusted estimates with 95% CI. (a) Professor D Julian A Scott, University of Leeds, 2010–12, personal communication; and (b) Mr Matthew J Bown, University of Leicester and the NIHR Cardiovascular Biomedical Research Unit, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

TABLE 10 Meta-analysis of the influence of cardiovascular drugs on small aneurysm growth rates

Drug	Number of studies	Unadjusted analyses				Adjusted analyses			
		Total number of patients	Estimate (SE) mm/year	p-value	I ² (%)	Total number of patients	Estimate (SE) mm/year	p-value	I ² (%)
ACE inhibitors	7	4826	-0.125 (0.143)	0.379	61	4269	0.002 (0.128)	0.986	42
Beta blockers	7	4824	-0.189 (0.076)	0.013	0	4269	-0.111 (0.083)	0.183	0
Calcium channel blockers	6	4124	-0.199 (0.082)	0.015	0	3723	-0.081 (0.088)	0.358	0
Statins/lipid-lowering drugs	6	4621	-0.341 (0.133)	0.010	47	4118	-0.205 (0.132)	0.121	32
Antiplatelets	6	4137	-0.187 (0.101)	0.065	32	3723	-0.125 (0.106)	0.241	19
Any antihypertensive	7	4826	-0.189 (0.064)	0.003	0	4271	-0.108 (0.075)	0.149	0

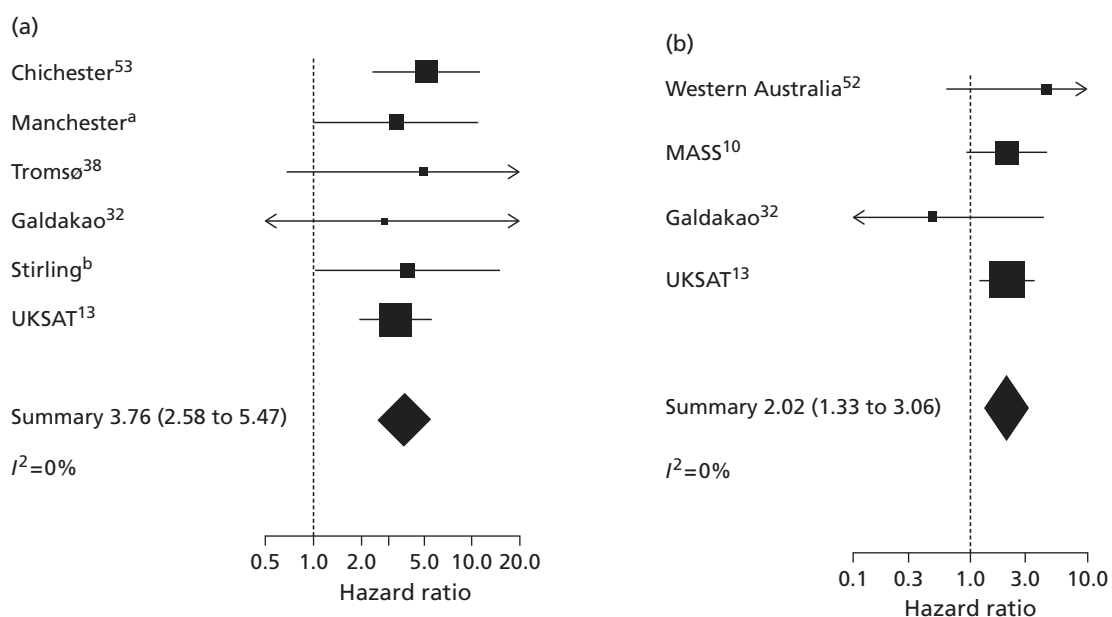


FIGURE 17 Effect of (a) sex (female vs. male) and (b) smoking (current vs. ex/never) on aneurysm rupture rates in individual studies and meta-analysis: HRs (95% CI) adjusted for aneurysm diameter. (a) Professor Charles N McCollum, University Hospital of South Manchester, 2010–12, personal communication; and (b) Mr Richard Holdsworth, Stirling Royal Infirmary, 2010–12, personal communication. UKSAT, United Kingdom Small Aneurysm Trial.

studies^{13,39,40,51,52,55} reported both rupture events and use of drugs. Of these, only two estimates, on average, could be obtained for each class of drug, none of which showed statistical significance (Table 12).

Inputs to health economic modelling

These IPD from 18 surveillance studies (see Table 6) were next used to provide inputs relating to growth and rupture rates for the health economic modelling, as described in Chapters 7 and 8.

TABLE 11 Meta-analysis of the influence of patient characteristics on small aneurysm rupture rates: HR (95% CI) adjusting for current aneurysm diameter

Characteristic	Number of studies	Number of AAA ruptures	HR (95% CI)	p-value	I ² (%)
Age at baseline (per year)	14	228	1.04 (1.01 to 1.07)	0.004	0
Calendar year at baseline (per year)	13	226	0.96 (0.92 to 1.00)	0.033	0
Sex (female vs. male)	6	141	3.76 (2.58 to 5.47)	<0.001	0
Smoking (current vs. ex/never)	4	103	2.02 (1.33 to 3.06)	0.001	0
BMI (per kg/m ²)	5	80	0.93 (0.88 to 0.99)	0.029	0
Diabetes	2	66	1.27 (0.45 to 3.54)	0.653	0
Mean arterial blood pressure (per 10 mmHg)	7	157	1.32 (1.11 to 1.56)	0.001	31
Pulse pressure (per 10 mmHg)	7	157	1.11 (1.02 to 1.22)	0.019	0
History of cardiovascular disease	3	73	1.32 (0.77 to 2.27)	0.319	0

TABLE 12 Influence of cardiovascular drugs on small aneurysm rupture rates in individual studies: HRs (95% CI) adjusting for current aneurysm diameter

Study	ACE inhibitors	Beta blockers	Calcium channel blockers	Statins/lipid-lowering drugs	Antiplatelets	Any antihypertensive
Western Australia ⁵²	1.25 (0.13 to 12.14)	a	1.94 (0.20 to 18.96)	0.66 (0.07 to 6.31)	a	0.42 (0.04 to 4.12)
PIVOTAL, USA ⁵¹	a	a		a	a	a
Propranolol, Canada ⁴⁰	a	1.99 (0.18 to 22.12)	6.03 (0.54 to 67.16)	2.33 (0.20 to 26.52)		0.77 (0.07 to 8.54)
Gävle, Sweden ³⁹	a	a	a	a	a	a
UKSAT, UK ¹³	1.17 (0.50 to 2.72)	1.28 (0.66 to 2.46)	1.42 (0.82 to 2.49)	a	0.83 (0.46 to 1.52)	1.08 (0.64 to 1.82)
Viborg, Denmark ⁵⁵	a	a	a		a	a

Blank cells indicate data not available.
a Not estimable because of low number of ruptures.

Chapter 7 Methods for cost-effectiveness analysis of alternative surveillance policies

In this chapter we describe the methods and preparatory work involved in assessing the cost-effectiveness of different surveillance policies. This includes how the information on small AAA growth rates and rupture rates from the IPD meta-analyses (see *Chapters 5* and *6*) is used to provide inputs for this health economic modelling. The results of the cost-effectiveness analyses are given in *Chapter 8*.

Introduction

Previous studies have estimated the cost-effectiveness of the screening strategy that was evaluated in the MASS trial. Estimates of the cost-effectiveness of this strategy have been adjusted over time, principally to reflect the emerging long-term data from the trial. The original cost-effectiveness estimates were based simply on 4 years of follow-up and estimated a mean cost per life-year gained within that truncated period of £28,400 (95% CI £15,000 to £146,000)⁵⁶ at 2000–1 prices. Using the observed data at 10 years of follow-up, the estimate had fallen to £7600 (95% CI £5100 to £13,000) despite revaluing costs to 2008–9 prices.⁴ Based on informal modelling, the original cost-effectiveness paper had suggested that the cost-effectiveness over 10 years would indeed be around £8000 per life-year saved.⁵⁶

However, it is clearly recognised that an investment in a screening programme needs to be assessed over a longer period that does not cut short the benefits from avoided aneurysm-related mortality and will require a formal model. Such a model, taking a 30-year perspective but initially based on the 4-year MASS results, was developed and this estimated the cost per life-year gained over a 30-year period as £2320 (with a 95% uncertainty interval of £1600 to £4240).⁸ As the period of follow-up of the MASS trial has extended, the uncertainty associated with the longer-term effects of screening has been reduced, and scope now exists to compare the model results at 10 years and as necessary to recalibrate the model to more accurately reflect the longer-term observed data.

All these estimates have assumed a screening programme in elderly men with a surveillance pattern of: no recall for patients with an aortic diameter of < 3.0 cm; yearly rescanning of patients with an aortic diameter of 3.0–4.4 cm; 3-monthly rescans for patients with an aortic diameter of 4.5–5.4 cm; and consideration for surgery if an aortic diameter of \geq 5.5 cm. This surveillance strategy adopted in MASS was based on the data available and expert clinical opinion at the time of the planning of the trial in 1995–6. The same pattern was subsequently adopted by the NAAASP. The analysis of growth and rupture rates in this RESCAN project provides an evidence base and opportunity to investigate whether or not a different surveillance strategy might be better than that used in MASS and subsequently by NAAASP.

Other economic models of AAA screening have of course been published. A systematic review of the models to 2006 emphasised the variability in their estimates of cost-effectiveness.⁵⁷ Since that review, a number of further modelling studies have been published drawing on data from a variety of sources: for example studies relating to Italy,¹⁵ to the Netherlands and Norway,⁵⁸ to Canada^{59,60} and to Denmark.⁶¹ These have all concluded that screening is acceptably cost-effective, with the exception of a study using data from Denmark and other sources, which concluded that screening did not seem to be cost-effective.⁶² A recent modelling study, again using Danish data, contradicts that previous conclusion, suggesting that screening men at age 65 years is highly cost-effective compared with no screening and, additionally, that rescreening after 5 years may be a cost-effective extension to the programme.⁶³ However, no models of cost-effectiveness of AAA screening have been published that have specific relevance to NAAASP, other than those already cited relating to and derived from the MASS study, which is the largest randomised trial of AAA screening and contributes most to the international evidence.⁷

The focus of the cost-effectiveness element of the current study is to analyse the implications of the RESCAN analyses, relating to the international evidence on growth rates and rupture rates, for the most cost-effective surveillance strategy following AAA screening. Cost-effectiveness is of course a function not only of these clinical parameters but also the behavioural, resource-use, and cost data relevant to a particular screening programme. Hence, we have chosen to use such country-specific data relevant to the current UK programme.

The work specifically undertaken on the model for this study consisted of the following elements:

1. Validation and recalibration of the previously published model⁸ to best reflect the accumulated 10-year follow-up data from MASS, including incorporation of time-dependent parameter values.
2. Adaption of the model structure to fully incorporate unobserved 'tunnel' states to reflect the growth and rupture probabilities for all aneurysms, whether or not reobserved and remeasured at a recall scan.
3. Re-estimation of current unit costs for screening interventions and elective and emergency surgery.
4. Incorporation of data from NAAASP, including attendance rates, prevalence of identified aneurysms, and distribution of aneurysm sizes at initial screening.
5. Incorporation of size-specific growth and rupture rates from the analysis of the IPD surveillance data sets reported in *Chapters 5 and 6*.

Each of these aspects of our development of the model is to enable us to address the issue of the cost-effectiveness of alternative surveillance strategies, in the context of the NAAASP, and each aspect is addressed in turn in this chapter.

The initial model

The starting point for the economic analysis in this project was the economic model that had previously been developed by members of the research team, to estimate the long-term cost-effectiveness of a screening programme using the MASS trial screening and surveillance protocol. Details of this model have previously been published.⁸ In summary, it used a Markov model, with 3-monthly cycles, to compare the introduction of a formal screening programme of an invitation for a one-off US scan for men aged 65 years, and the MASS surveillance strategy described above if an aneurysm is identified, with the policy of no systematic screening. The original model is represented in *Figure 18*.

The model used a 30-year time horizon (so approximating lifetime results). The methods were consistent with those recommended for the National Institute for Health and Care Excellence (NICE)'s Technology Appraisal Programme.⁶⁴ The cost perspective was that of the NHS and the model estimated life-years gained and adjusted these for age-specific utility values relating to the UK population to provide ICERs in terms of QALYs.

For this model, parameter values were estimated from patient-level data from the 4-year analysis of the MASS study and the model structure was internally validated by comparing its results against observed event and cost-effectiveness data over the 4-year time period. In addition, it was externally validated against key outcomes from the Cochrane review of AAA screening and surveillance.⁷

Validation and recalibration of the previously published model to better reflect the 10-year follow-up data from the Multi-centre Aneurysm Screening Study

The first step in the current study was to revalidate the model comparing the 10-year model outcomes against the 10-year observed data from the follow-up of MASS, and, where necessary, to adjust or 'recalibrate' the model parameters to better reflect that observed data. We used the 8.9–11.2 years of observed follow-up (mean 10.1 years) to better estimate the values for the parameterisation of the economic

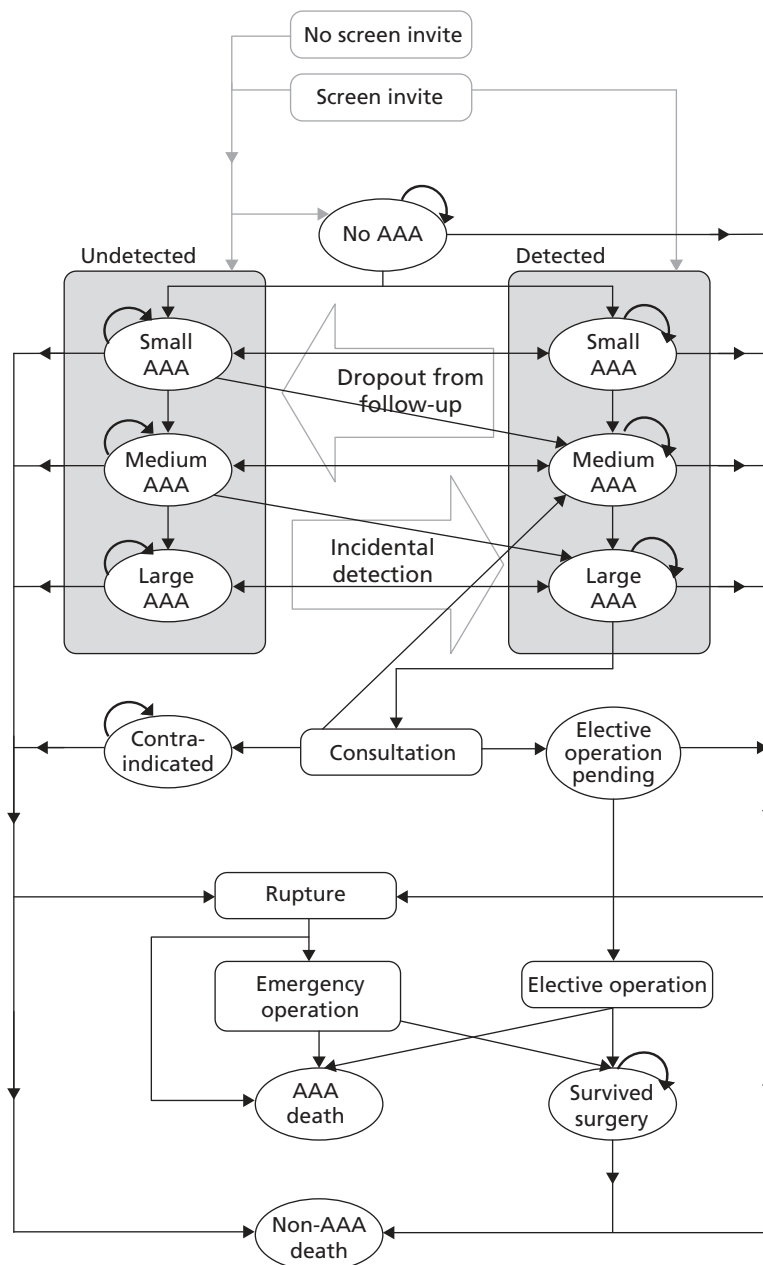


FIGURE 18 Original health economic model structure. Reproduced with permission from figure 1 of Kim LG, Thompson SG, Briggs AH, Buxton MJ, Campbell HE. How cost-effective is screening for abdominal aortic aneurysms? *J Med Screen* 2007;14:46–52. <http://dx.doi.org/10.1258/096914107780154477>.⁸

model. Outputs of the model were compared against those observed in the trial, by considering the numbers of key observed events and cost-effectiveness results at the end of this follow-up period.

Given the staggered recruitment of participants into the trial and the range of follow-up periods for individual patients, for the purpose of comparing numbers of key events the model replicated censoring patterns by removing equal proportions as observed in the trial of numbers in each state for every 3-month cycle, so that the total person-years of follow-up were comparable. The model was then run over 11.25 years to provide comparability. To produce estimates of costs and life-years at 10 years comparable with those observed in MASS, the model was run for 10 years with costs based on 2008–9 prices and survival based on all-cause mortality. Given the characteristics of the MASS trial population, it might be expected that mortality

rates would not be comparable with the national statistics, and so for the internal validation exercise MASS-specific mortality data were used to estimate the probability of mortality in each 3-month cycle, rather than using national mortality statistics that were incorporated into the model to give it greater external validity or generalisability.

Initially the model did not appear to perform particularly well against observed data in terms of key events or cost-effectiveness results over the longer follow-up period. As the length of follow-up had increased, trends may have emerged in key parameter values and differences between modelling and observed outputs could be partly attributed to the use of time-constant parameters. Time-dependent transition probabilities were therefore estimated using 'logistic' and 'Poisson' regressions, to improve the fit of the model. The differences between the observed and modelled data may also have been in part due to parameters used to inform the modelling that could not be observed in MASS. In particular, two parameters, the probability of opportunistic detection among those not in active screening and the rupture rate of undetected large aneurysms, were seen as potentially unreliable. The first had been based on calculations utilising data from the control arm of the trial, to give a crude estimate of the detection rate. The latter had been estimated to fit the 4-year data, assuming it lay between the rupture rate in detected large aneurysms and the rupture rate among aneurysms contraindicated for elective surgery. A recalibration exercise was conducted using a range of figures for both these parameters, to obtain model results that gave more similar numbers of key events (i.e. elective operations, emergency operations and AAA deaths) to those observed in MASS.

It was not easy to achieve complete consistency between the observed and modelled clinical outcomes. Given that the long-term ICER was the primary outcome for the cost-effectiveness modelling, the recalibration focused on eliminating disparities in the modelled and observed differences between the arms.

Table 13 shows key event rates as observed in MASS, as estimated by the original model and as estimated by the model following recalibration. The pattern of events over time from the observed data, the initial model estimates and the recalibrated estimates are shown in *Figure 19a–h*.

This recalibration process achieved similarity between the modelled and observed differences in key events between the arms, as well as in the resultant ICERs (*Table 14*). The ICER was £7600 per life-year based on observed 10-year data: the original model estimated an ICER at 10 years of £18,000, the recalibrated model estimated the ICER at £8900, closer to that from the observed data. This suggested that, though imperfect, the model would be suitable for extrapolation of cost-effectiveness results over the long term.

Adapting the model structure to fully incorporate unobserved 'tunnel' states

The previously constructed Markov model⁸ needed adaptation to account more explicitly for the incidence of rescans. The original model, with 3-monthly cycles, was built with a view to considering one surveillance policy (that pertaining to the MASS data of yearly recall for AAAs measuring 3.0–4.4 cm and 3-monthly recall for medium AAAs measuring 4.5–5.4 cm). The model averaged out the surveillance for the smaller aneurysms, effectively assuming that surveillance scans were being conducted every cycle but assigning only one-quarter of the rescan costs to each cycle. This meant that individuals were able to transition to larger aneurysmal states in each 3-month cycle and on reaching the large state they could be considered for elective surgery or returned to screening. However, in reality, those in a small AAA state (3.0–4.4 cm) are not rescanned every cycle and cannot move into the surveillance pattern for a larger aneurysm until the increased size of their aneurysm has been identified through a scan. In the original model, costs associated with rescanning were averaged across the cycles, 0.25 of a rescan cost per cycle for the small aneurysmal state and assigned as one per cycle for the medium-sized AAA. Although this approximation was adequate when considering the one surveillance strategy, the model needed to be adapted for the purposes of answering questions around different surveillance policies.

TABLE 13 Comparison of key events observed in MASS and economic model

10-year cumulative key events			
	Observed in MASS ^a	Original model ^b	Model after recalibration ^c
Control group			
Elective operations	226	256	213
Emergency operations	141	140	168
AAA deaths	296	305	385
Non-AAA deaths	10,185	10,139	10,148
Invited group			
Elective operations	552	607	539
Emergency operations	62	88	97
AAA deaths	155	202	248
Non-AAA deaths	10,119	10,185	10,189
Difference between invited and control groups			
Elective operations	326	351	326
Emergency operations	-79	-52	-71
AAA deaths	-141	-103	-137
Non-AAA deaths	-66	46	41

a Key events observed in MASS at 10-year follow-up.
 b Economic model using time-constant parameter estimates from MASS 10-year follow-up.
 c Economic model, with time-dependent parameter estimates from MASS 10-year follow-up and post-calibration exercise.

This adaption was achieved through the inclusion of 'tunnel' states for aneurysm growth, accounting for patients in whom aneurysm growth occurred but was not observed or acted on. The structure of the extended model is represented diagrammatically in *Figure 20*. These tunnel states allow aneurysms to grow in between scans, where the individual is subject to the relevant rupture rate. An individual can stay in the tunnel state that they have entered in subsequent cycles, or transition to larger AAA tunnel states. Only when a scheduled surveillance scan occurs are individuals then able to be move out of these unobserved tunnel states into observed states. On this they can then be subject to more frequent scanning, or events that occur as a result of entering the large AAA state (i.e. consideration for elective surgery). This provides a more accurate representation of reality and most importantly can allow for the effects of differing policies by adjusting the number of cycles that individuals spend in these states before a rescan and a return to observed states. Aneurysms that are detected opportunistically are assumed to enter an observed state before moving into tunnel states. However, given that this opportunistic detection can occur in every cycle, an approximation in the cycles immediately following opportunistic detection is used to bring these individuals into the same rescanning schedule as the rest of the detected aneurysm cohort. This retains programming efficiency and has the effect that some opportunistically detected patients will be assumed to receive their first 1-year scans after a shorter period than a full year.

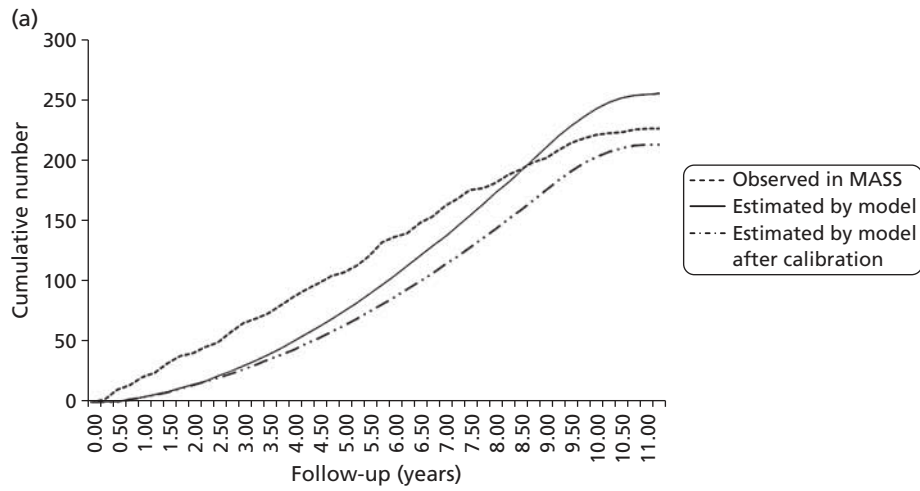


FIGURE 19a Number of elective operations in control group over 10 years' (mean) follow-up.

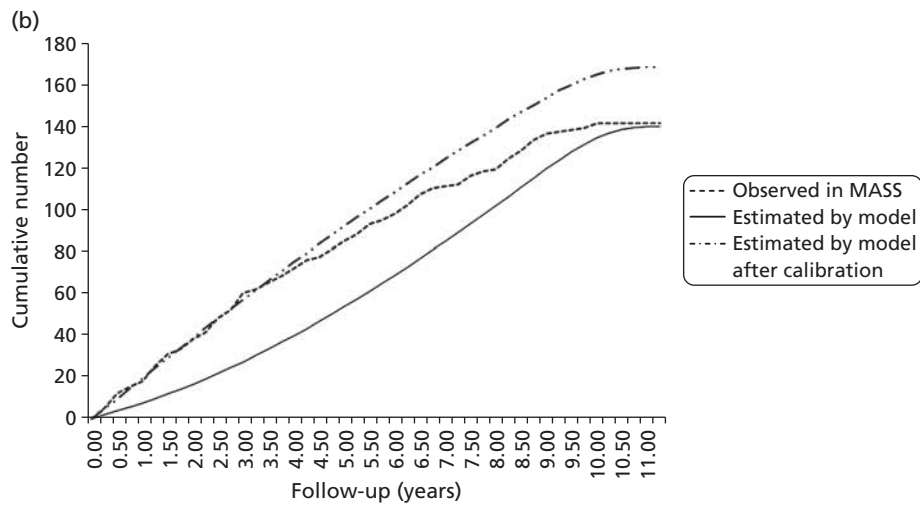


FIGURE 19b Number of emergency operations in control group over 10 years' (mean) follow-up.

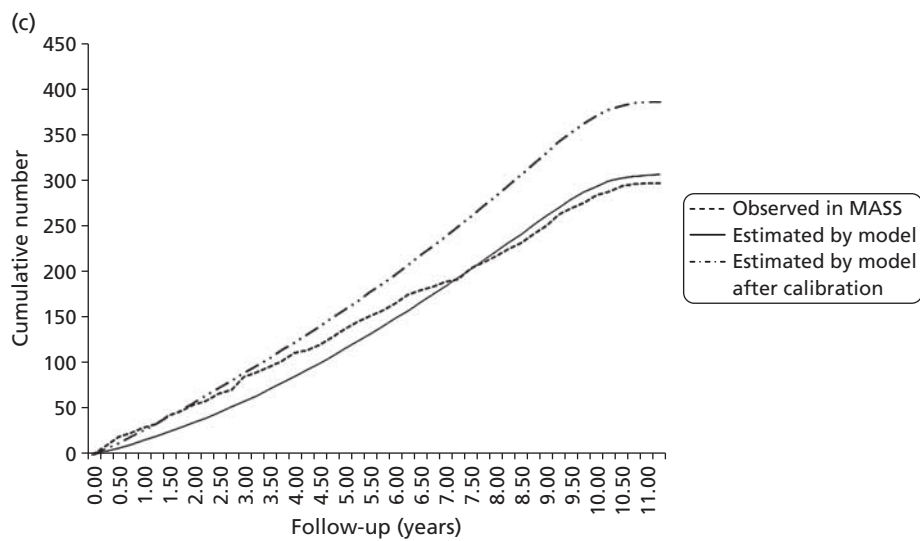


FIGURE 19c Number of AAA-related deaths in control group over 10 years' (mean) follow-up.

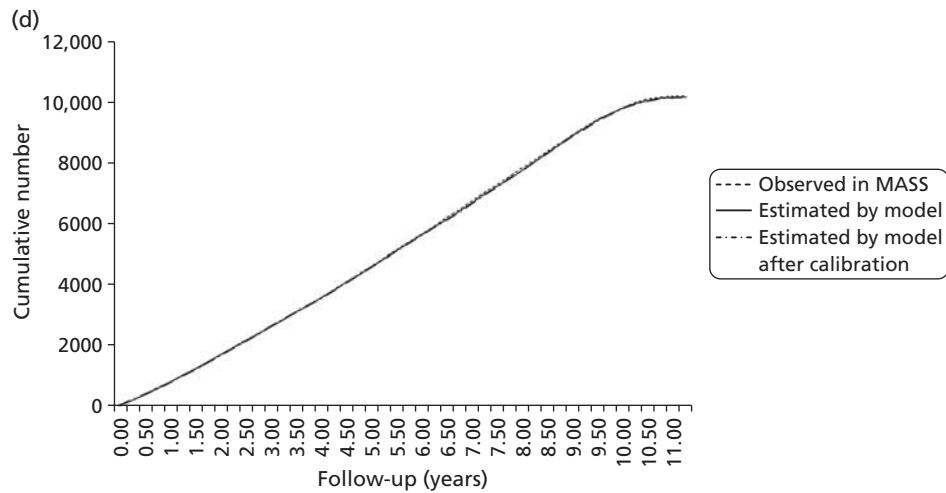


FIGURE 19d Number of non-AAA deaths in control group over 10 years' (mean) follow-up.

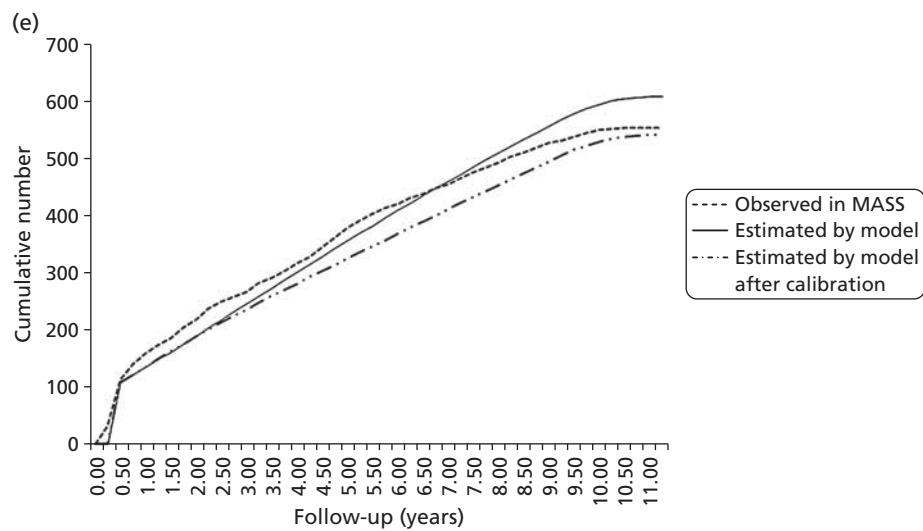


FIGURE 19e Number of elective operations in invited group over 10 years' (mean) follow-up.

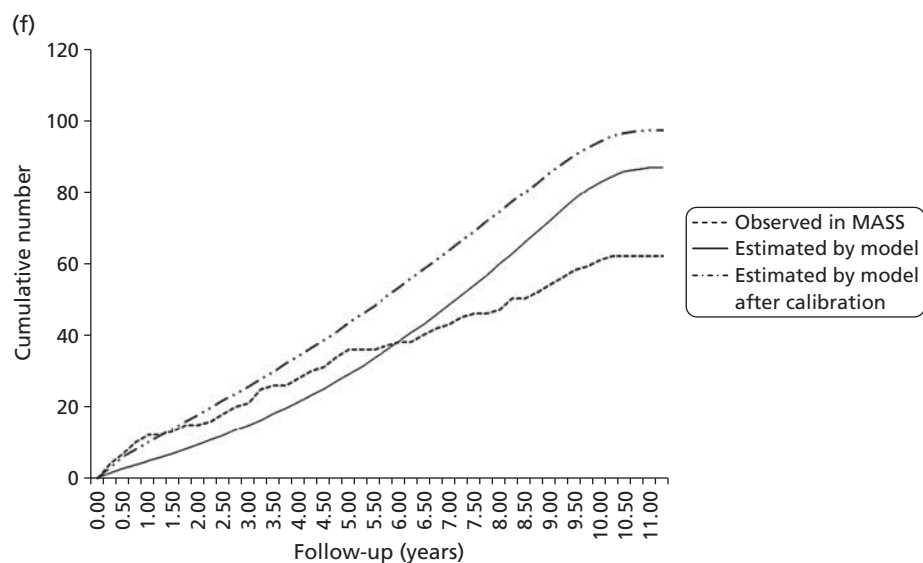


FIGURE 19f Number of emergency operations in invited group over 10 years' (mean) follow-up.

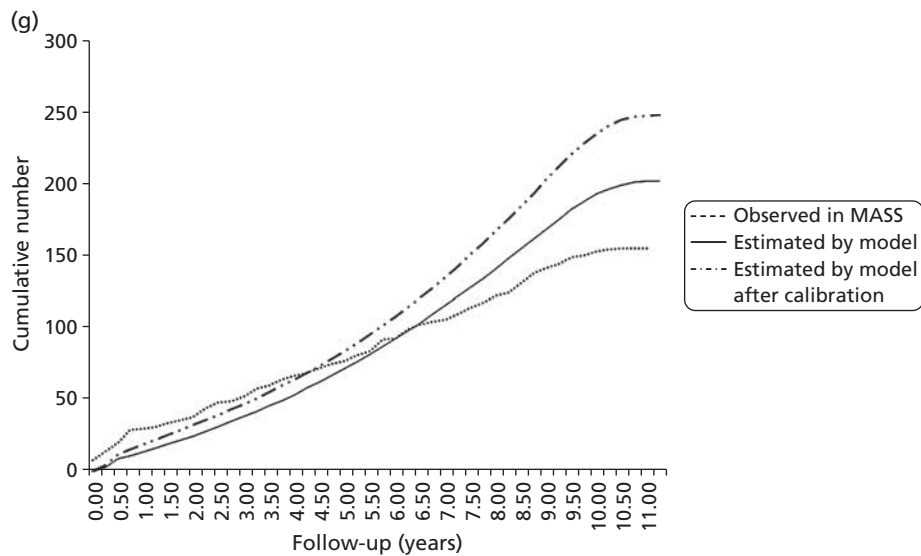


FIGURE 19g Number of AAA-related deaths in invited group over 10 years' (mean) follow-up.

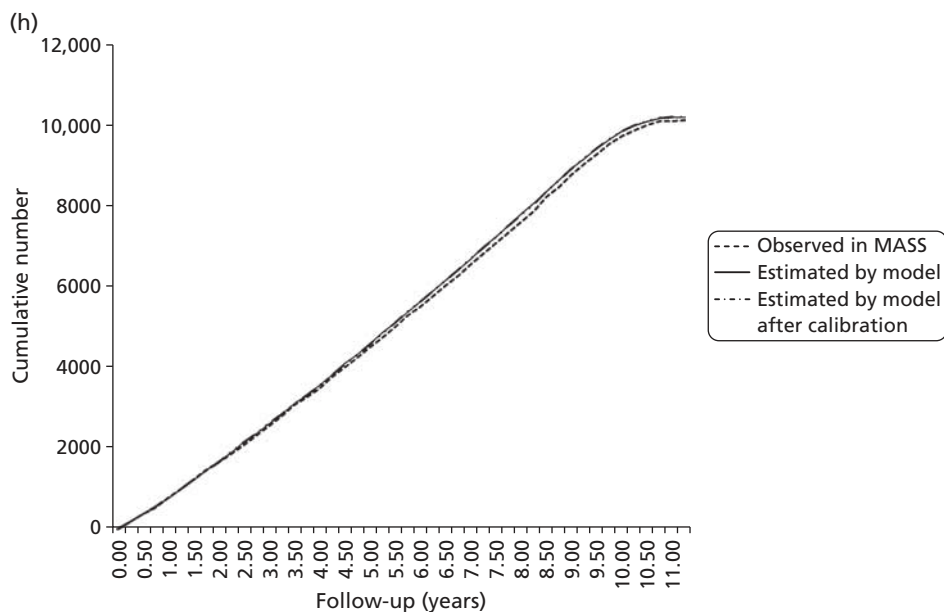


FIGURE 19h Number of non-AAA deaths in control group over 10 years' (mean) follow-up.

It may be useful to consider the current screening policy of 1 year and 3 months for small and medium AAAs, respectively, as an example of the way the new structure works. An individual invited to and having attended screening, with a small aneurysm observed at baseline, would be invited to return for another scan in 1 year, equivalent to four cycles in the model. Assuming the AAA had not grown, nor ruptured and the individual had not dropped out of surveillance or died, they would move into the small (unobserved) tunnel state in cycle 2. If no transition had occurred in cycles 3 and 4, the individual would then move out of the small unobserved 'tunnel' state back into the small observed state where a rescan takes place. They would then move into tunnel states again following this scan. Alternatively, the aneurysm could have grown and the patient transitions into the tunnel state for medium aneurysms in cycle 2 and possibly into the tunnel state for large aneurysms in cycle 3. The tunnel states mean that this individual will not be treated as having a large aneurysm as regards the surveillance policy until this growth has been observed at the next scan in cycle 4.

TABLE 14 Comparison of discounted mean costs and effects observed in MASS and estimated in economic model

Cost-effectiveness at 10 years ^a			
	Observed in MASS	Original model	Model after recalibration
Control group			
Life-years (mean)	7.509	7.291	7.282
Cost, £ (mean)	108	118	124
Invited group			
Life-years (mean)	7.523	7.297	7.293
Cost, £ (mean)	208	233	225
Difference between invited and control groups			
Difference in life-years, £ (mean)	0.014	0.006	0.011
Difference in costs, £ (mean)	100	115	101
ICER (life-years), £	7600	18,000	8900
ICER (QALYs), £ ^b	9700	23,000	11,400

a Costs based on 2008–9 prices; costs and mortality discounted at 3.5%. Survival based on all-cause mortality.

b Life-years adjusted using population norms.

These techniques for modelling growth also mean that the accrual of costs due to rescanning should be more accurate. Costs will accrue as rescans occur over time, as opposed to averaging costs over a number of cycles. By implementing these changes the model can be used to investigate a range of potential new surveillance policies and compare their cost-effectiveness.

Re-estimation of current unit costs for screening interventions, and elective and emergency surgery

The various estimates of cost-effectiveness based on MASS, referred to earlier, have so far all used original unit cost estimates at 2000–1 prices, updated as necessary only for general health service inflation. There was a clear need for a more thorough update of costs to reflect a range of changes in practice. All costs were re-estimated at 2010–11 price levels.

Screening intervention costs

The original costs for the elements of screening came directly from the costs of the services in the trial. These have now been superseded by costs directly provided by the NAAASP. *Table 15* shows the original figures, those figures updated to 2010–11 price levels, and the current unit costs, again at 2010–11 price levels from the NAAASP.

Costs for elective and emergency aneurysm repair

The MASS estimates for the cost of elective and emergency procedures were calculated using very detailed bottom-up costing using patient notes and other detailed hospital records of 577 patients from the four surgery centres involved in the MASS study.⁵⁶ It was not feasible to re-estimate the costs using the same resource-intensive methods for this study. Rather we chose to estimate unit costs for surgery using more recent published studies where available and where more recent, relevant studies were not available by making explicit adjustments to the mean per patient costs previously calculated to reflect more recent routine data on resource use.

The most recent and largest (sample size) costing exercise was completed as part of the analysis of the endovascular aneurysm repair (EVAR)-1 trial, which we have used to estimate the costs of open repair and

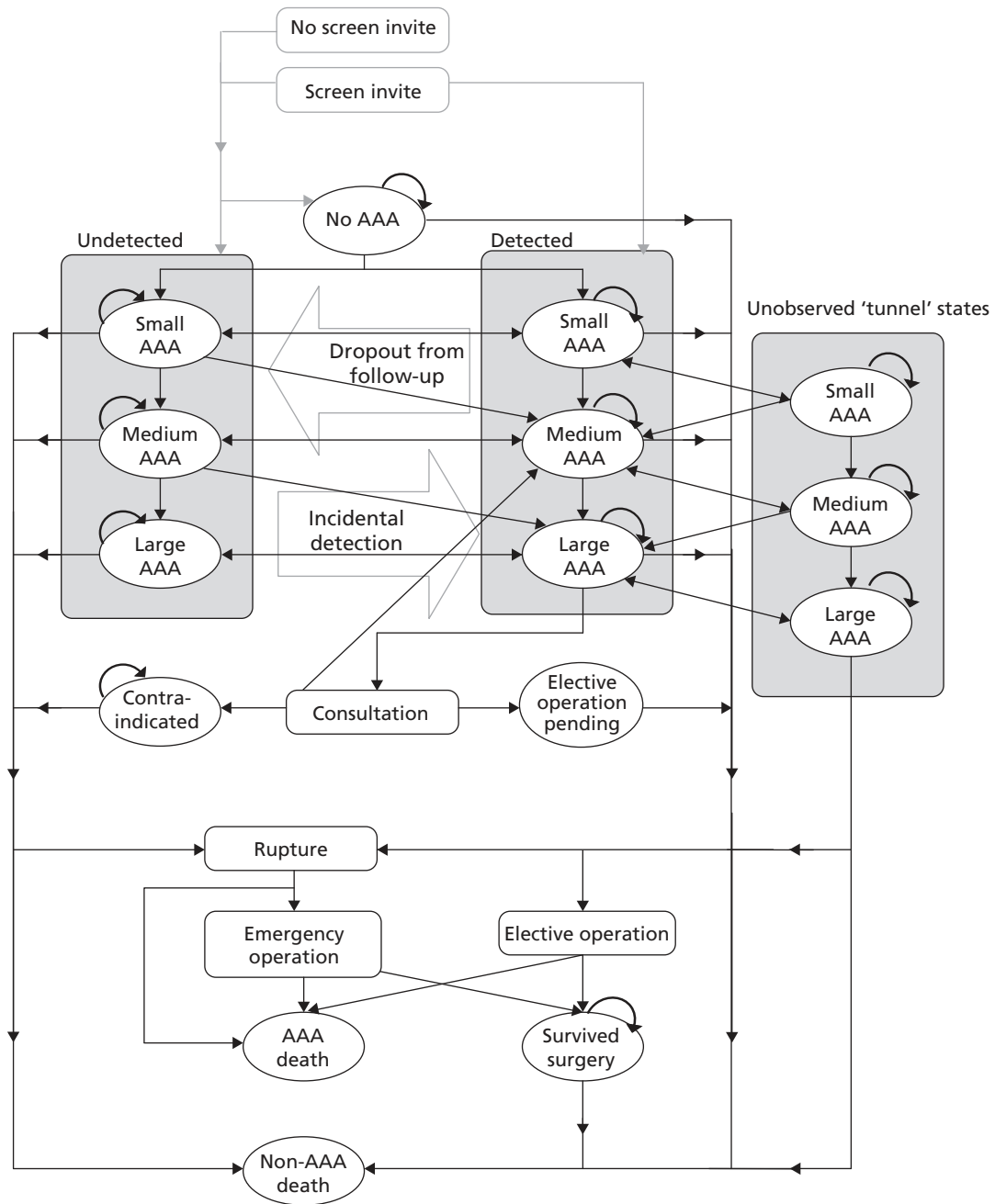


FIGURE 20 Extension of original model structure to include unobserved 'tunnel' states.

endovascular repair in an elective setting.⁶⁵ As per NICE guidance,⁶⁶ we assumed that emergency EVAR operations are only being performed in a research environment and, so, we have only included costs for open emergency repair in our estimates. For emergency open repair an estimate of per patient costs was updated from the MASS trial, in the following way:

- (a) First, the major costs components were removed from the total mean per patient estimates for elective open repair and elective EVAR (from EVAR 1 trial⁶⁵ estimates) and emergency OR (from MASS trial⁶⁶ cost estimates). In each case, this constituted the removal of costs attributable to hospital stay and operation time. For EVAR this also included the cost of the stent. This cost was updated using more recent data from centres involved in the screening programme and correspondence with manufacturers.

TABLE 15 Costs for elements of screening

Element	Original MASS ⁵⁶ cost 2000–1 (£)	MASS ⁵⁶ cost inflated to 2010–11 (£)	Updated unit cost ^a (£)
Invitation to screen	1.31	1.84	1.70
Cost of first scan	19.08	26.80	32.20
Surveillance scan	46.04	64.67	68.00

a Source: UK NAAASP, personal communication, 2012.

- (b) The residual cost, made up of more minor resource-use items, such as blood products used and consumables, was inflated to 2010–11 prices according to Personal Social Services Research Unit indices.⁶⁷
- (c) The resource-use data were then updated for operation length and total hospital stay (apportioned using the same proportions for intensive care unit (ICU) and normal ward as had been observed in EVAR 1 trial or MASS, respectively) using recent data provided for us from the National Vascular Database (January 9 March 2012).⁶⁸ New unit costs for ICU, high-dependency unit (HDU) and vascular ward stay were all obtained from NHS reference costs for 2010–11.⁶⁹ A new unit cost estimate per hour of time in operating theatre was obtained.⁷⁰ These updated estimates were applied to the new resource-use estimates.
- (d) The elective cost has been weighted according to the proportion of cases that are EVAR and OR in the National Vascular Database sample (approximately 70/30 for EVAR and OR, respectively).

Tables 16–18 illustrate this process for updated components of resource use and unit costs, for elective open, elective EVAR, and for emergency procedures, respectively. Tables 19–21 show the magnitude of the residual component of each of these three costs, which was simply inflated to 2010–11 prices. Table 22 summarises

TABLE 16 Components of resource use and unit costs for elective open repair

Component	EVAR 1 ⁶⁵ resource use	EVAR 1 ⁶⁵ unit cost (£)	Updated resource use	Updated unit cost (£)
Theatre time	215 minutes	17.58	181.97 minutes	20.67
HDU	1.88 days	832.00	1.65 days	883.00
ITU	2.47 days	1165.00	2.16 days	1226.00
Vascular ward	11.41 days	268.00	9.98 days	266.00
Total days	15.76 days		13.79 days	

TABLE 17 Components of resource use and unit costs for elective EVAR

Component	EVAR 1 ⁶⁵ resource use	EVAR 1 ⁶⁵ unit cost (£)	Updated resource use	Updated unit cost (£)
Theatre time	191 minutes	17.58	147.04 minutes	20.67
HDU	0.83 days	832.00	0.63 days	883.00
ITU	0.59 days	1165.00	0.44 days	1226.00
Vascular ward	8.34 days	268.00	6.29 days	266.00
Total days	9.76 days		7.36 days	
Stent cost		5219.00		6500.00

TABLE 18 Components of resource use and unit costs for emergency open repair

Component	MASS trial ⁵⁶ resource use	Updated resource use	Updated unit cost (£)
Theatre time	182 minutes	161.94 minutes	20.67
ITU	4.74 days	7.12 days	1226.00
Vascular ward	7.66 days	11.51 days	266.00
Total days	12.4 days	18.63 days	

TABLE 19 Calculation of residual costs component inflated to 2010–11 prices for elective open repair

Component	Residual cost (£)
Total open repair cost as per EVAR 1 trial ⁶⁵	11,842
Length of stay component	7214
Operation time component	3647
Total of components	10,861
Residual costs to inflate	981
Residual costs inflated to 2010–11 prices	1014

TABLE 20 Calculation of residual costs component inflated to 2010–11 prices for elective EVAR

Component	Residual cost (£)
Total EVAR cost as per EVAR 1 ⁶⁵	13,019
EVAR stent and parts component	5219
Length of stay component	3543
Operation time component	3255
Total of components	12,017
Residual costs to inflate	1002
Residual cost inflated to 2010–11 prices	1036

TABLE 21 Calculation of residual costs component inflated to 2010–11 prices for emergency open repair

Component	Residual cost (£)
Total open repair cost as per MASS ⁵⁶	11,176
Length of stay component	6932
Operation time component	794
Total of components	7726
Residual costs to inflate	3450
Residual cost inflated to 2010–11 prices	4846

TABLE 22 Summary of updated unit costs for surgical procedures

Type of surgery	Updated cost per patient (£)	Cost per patient (EVAR 1 ⁶⁵) (£)	Cost per patient inflated to 2010–11 prices (EVAR 1 ⁶⁵) (£)	Cost per patient (MASS ⁵⁶) (£)	Cost per patient inflated to 2010–11 prices (MASS ⁵⁶) (£)
Elective OR	11,532.69	11,842.00	12,241.17	6909.00	9704.24
Elective EVAR	13,345.66	13,019.00	13,457.84		
Elective weighted	12,806.21				
Emergency OR	19,984.75			11,176.00	15,697.59

the new cost estimates and compares them with the original estimates, and the original estimates inflated to 2010–11 prices.

Costs of pre-surgical consultations

No newer estimates were available for the costs of consultations when referred to surgery which included costs of associated tests. The original MASS⁵⁶ estimates for these costs were simply inflated from 2000–1 to 2010–11 prices (£309.88 inflated to £435.25).

Incorporating data from the NHS Abdominal Aortic Aneurysm Screening Programme

To reflect current AAA screening in the UK, data from the NAAASP were utilised in the economic modelling. The attendance rate from those invited to screening in the NAAASP has been lower than that of the MASS trial (which was 83%); a figure of 73% from the NAAASP has been used in the modelling.⁷¹ A lower prevalence of AAAs has also been noted in data from the NAAASP, which might have some effect on cost-effectiveness results. In the MASS trial the prevalence was 4.9%, but the current prevalence observed in the NAAASP is 1.6% and this rate was used in the modelling. Data were provided to us from the NAAASP on the distribution of aneurysm sizes detected in the screening programme, to reflect possible changes in aneurysm sizes observed at baseline compared with the MASS data used in the original model.

In addition, non-AAA mortality rates were estimated using data from Hospital Episodes Statistics⁷² and the Office for National Statistics (ONS) for 2010,⁷³ incorporated into the modelling as age-specific 3-month probabilities.

Incorporating size-specific growth and rupture rates from the RESCAN analyses

Growth rates

From the reanalysis of existing surveillance data (see *Chapter 6*) we have developed random-effects models to describe AAA growth in each of the studies. These models are utilised to calculate how individuals pass through the size states of the Markov model used for the cost-effectiveness modelling. The methods are described fully in *Appendix 4*, with a summary given here.

Firstly, 3-month transition probabilities were calculated between 5-mm-wide size states (3.0–3.4 cm, 3.5–3.9 cm, 4.0–4.4 cm, 4.5–4.9 cm, 5.0–5.4 cm and 5.5+ cm). To achieve this, a cohort is envisaged with screening distribution of small aneurysm sizes taken from the Chichester screening study (shown to have an almost identical distribution to the NAAASP small diameters, as shown in *Figure 21*). This distribution is skewed towards small aneurysms with the mode close to 3.0 cm. The aneurysms in this envisaged cohort are

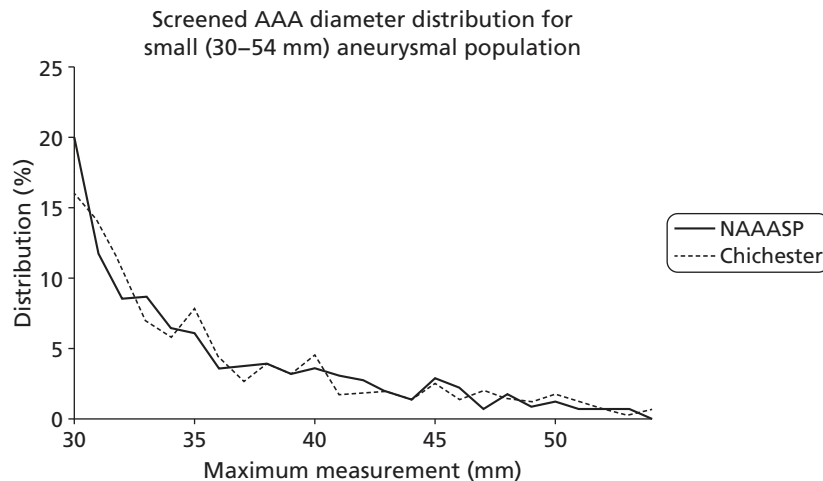


FIGURE 21 Distribution of AAA diameter at first screen from NAAASP data and Chichester Screening Programme data.

then allowed to grow over time using the baseline size-specific growth rates estimated from each study separately. For any 3-month period following screening, the estimated occupancy probabilities in each 5-mm-wide size state were calculated using the predictive distribution of aneurysm sizes. Those screened as normal are assumed to account for 98.3% of the screened population⁹ and are also allowed to grow, with an estimated 0.207% reaching 3.0 cm every 3 months and, thereafter, growing at a rate equivalent to a screen detected patient with baseline diameter 3.0 cm. The occupancy probabilities from the cohort are then used to calculate 3-month transition probabilities between size states using the Chapman–Kolmogorov equations and assuming a progressive only Markov model.⁷⁴ The log-odds of the transition probabilities for each 3 months over a 30-year time period after screening are obtained together with their SEs, and these study-specific estimates are then pooled in a second stage using random-effects meta-analysis.

'Equivalence' probabilities

Different choices of small aneurysm states are considered in the Markov transition models to allow comparisons of different screening strategies. It is therefore necessary to calculate 3-month transition probabilities between any size states of interest. Given the 3-month transition probabilities calculated above for the 5-mm-wide size states we can obtain 'equivalent' transition probabilities for any concatenation of these states (e.g. 3.0–4.4 cm, 4.5–5.4 cm, 5.5+ cm). These 'equivalence' probabilities are defined by the requirement that two Markov models with different small aneurysm size states produce the same proportion of large aneurysms (> 5.5 cm) over time if no external intervention, deaths or censoring takes place. Hence, this facilitates a fair comparison of the different surveillance strategies since the rate of growth to large AAAs without intervention will be the same across all models. The method used to calculate these 'equivalence' probabilities is described in *Appendix 4*.

Rupture rates

To obtain 3-month transition probabilities of rupture over a 30-year time period, as required by the health economic model, we fit a parametric survival model to the data in each study. Only men are considered for this analysis (since men are the focus of the screening policy). Specifically, a Weibull proportional hazards model with time-updated covariate (AAA diameter) is used. Events other than rupture that terminate follow-up (lost to follow-up, non-rupture-related death or surgery) are classified as censored observations. The (transition) probability of rupturing over any 3-month time period given AAA diameter at the beginning of the period is then approximated from the survival distribution. The log-odds of these probabilities are obtained together with their SEs, and these study-specific estimates are pooled in a second stage using random-effects meta-analysis.

Analysis of cost-effectiveness using the adapted and updated model

These developments enable us to use the model to estimate the life-years, QALYs, costs and net monetary benefits for a series of strategies with different recall frequencies, compared initially with the base case of the existing strategy, and by looking at differences in net benefit to extend to comparisons between any two strategies.

In this particular context, a probabilistic sensitivity analysis (PSA), as might typically be provided as a representation of the overall uncertainty in the estimates of cost-effectiveness, would not adequately characterise that overall uncertainty. In particular, it is not readily feasible to estimate the correlated uncertainty around the very many (480) age- and size-related aneurysm growth and rupture rates derived from the IPD meta-analysis incorporated into the model, or to provide evidence-based estimates of uncertainty distributions around other parameters, or to characterise the underlying structural uncertainty in this complex model. Therefore, rather than provide a potentially misleading PSA, we have chosen to employ simple one-way sensitivity analyses to characterise the effects on net benefit of uncertainty around growth rate and rupture rate estimates, and to check whether or not the conclusions regarding the preferred strategy are sensitive to this uncertainty. For comparison we illustrate the effects of uncertainty around other important parameters in the model.

Chapter 8 Results of cost-effectiveness analysis of alternative surveillance policies

The current surveillance strategy used in the NAAASP follows that of the MASS trial. The strategy was based on the expert judgement informed by the limited data available at the planning stage of the trial. The analysis in this study of growth rates and rupture rates enable us now to analyse the cost-effectiveness of alternative surveillance in terms of the frequency of recall for men screened as having an aneurysm between 3.0 and 5.4 cm.

In this chapter we present the comparative cost-effectiveness of a number of alternative surveillance strategies using the revalidated, and extended model with updated unit costs and key characteristics from the NAAASP (uptake rates and distribution of aneurysm sizes at screening).

Alternative surveillance strategies

We used the adapted and updated model described in *Chapter 7* to examine the health benefits (in terms of life-years) and overall costs, modelled over a 30-year period, for a range of alternative surveillance strategies as compared with the current strategy which we refer to as strategy A. *Table 23* summarises the values and sources of clinical and cost parameters used. The alternative strategies included both lengthening and shortening the current time intervals between rescans for those identified with aneurysms between 3.0 and 4.4 cm (base case 1 year) and 4.5 and 5.4 cm (base case 3 months). We assumed that a recall more frequent than 3 months would be unworkable, so did not consider any such options. In analysing any of the different surveillance strategies we assume that the same strategy would also apply to all opportunistically identified aneurysms in both arms. This assumption explains the very small difference in the control arm life-years and cost between strategies.

Table 24 sets out the key comparison, which is illustrated on the cost-effectiveness plane in *Figure 22*. Strategy A represents the base case of the current screening strategy, with an ICER against no formal screening of £5572 per life-year gained and £7143 per QALY gained. To identify whether or not an alternative strategy was an improvement, and which was best, we focused on the ICERs (for both life-years and QALYs) and the net monetary benefit calculated as $(\text{Net QALYs} \times £20,000) - \text{Net costs}$. We used the threshold value of £20,000 per QALY to be consistent with the opportunity cost of interventions within the NHS as articulated by NICE.⁷⁵

Each of the alternative strategies demonstrated appropriate directional changes in the life-years gained from screening and the QALYs gained from screening. The strategies, which extend one or more intervals, slightly reduce the QALY gain (by missing a small proportion of aneurysms that would go on to rupture) and slightly reduce the cost (by avoiding additional scans), whereas strategies that decrease intervals increase the QALY gain and increase the costs. This effect is shown in *Figure 22*, where the strategies that increase intervals (strategies B, C, D and G) fall in the south-west quadrant of the cost-effectiveness plane (where both costs and QALYs are reduced), whereas a strategy that decrease intervals (strategy E) falls in the north-east quadrant (where both QALYs and costs increase). Strategy F, in which all aneurysms between 3.0 and 5.5 cm are recalled at 6-monthly intervals, can be eliminated from further consideration in that it reduces QALYs and increases costs, so is dominated by existing strategy A which is clinically more effective and cheaper.

The economic question for strategy E is whether or not the increase in QALYs is sufficient to justify the increase in costs, while for each of strategies B, C, D and G it is whether or not the reductions in cost are sufficient to compensate for the QALY losses. This is assessed against a view of the acceptable cost per QALY or threshold. Using the threshold of £20,000 per QALY, we can see that strategy E far exceeds the acceptable threshold and is not cost-effective. Given the only other practical strategy, to increase frequency

TABLE 23 Parameter estimates for adapted economic model

Clinical parameters	Estimate	Source
Proportion reinvited to screening	0.1360	MASS ⁸
AAAs at first screen – attenders	0.0166	NAAASP ⁷¹
AAAs at first screen – non-attenders	0.0166	NAAASP ⁷¹
Non visualised AAAs	0.0166	NAAASP ⁷¹
Proportion of scans non-visualised	0.0121	MASS ⁸
Proportion of screen invited attending	0.730	NAAASP ⁷¹
Proportion of AAAs at first screen – small	0.809	NAAASP ⁷¹
Proportion of AAAs at first screen – medium	0.106	NAAASP ⁷¹
Proportion of AAAs at first screen – large	0.0854	NAAASP ⁷¹
Transition probabilities (3-monthly)		
Grow from no AAA to small AAA	0.00207	Chichester ⁵³
Grow from small AAA to medium AAA	TDTP ^a	RESCAN
Grow from medium AAA to large AAA	TDTP	RESCAN
Probability of dropout	0.0142	MASS
Rupture probability – no AAA	0	Assumption
Rupture probability – small AAA	TDTP	RESCAN
Rupture probability – medium AAA	TDTP	RESCAN
Rupture probability – detected large AAA	0.0125	MASS
Rupture probability – undetected large AAA	0.0282	Calibration
Rupture probability – contraindicated for surgery	0.0282	MASS
Probability of opportunistic detection	0.0114	Calibration
Probability of emergency surgery following rupture	0.368	MASS
Probability of death following emergency surgery	0.342	MASS
Proportion of large AAAs receiving surgery	0.681	MASS
Proportion of large AAAs returned to screening	0.221	MASS
Proportion of large AAAs contraindicated for elective surgery	0.0977	MASS
Probability of death following elective surgery – screen detected	0.0298	MASS
Probability of death following elective surgery – opportunistically detected	0.0717	MASS
All-cause mortality – contraindicated for surgery	0.0599	MASS
Age-specific all-cause mortality	Age specific	ONS ⁷³
Cost parameters		
Invitation to screen (£)	1.70	See Chapter 7
Cost of first scan (£)	32.20	See Chapter 7
Surveillance scan (£)	68.00	See Chapter 7
Pre-surgical consultation (£)	435.25	See Chapter 7
Elective repair (£)	12,806.21	See Chapter 7
Emergency repair (£)	19,984.75	See Chapter 7

TDTP, time-dependent transition probabilities.

a Time-dependent transition probabilities, applied to each 3-month cycle.

of scans, strategy F, was dominated by the present screening strategy, we can conclude that decreasing recall intervals is unlikely to be cost-effective. Looking at the strategies (B, C, D and G) that increase screening intervals, we are seeking a strategy that releases at least £20,000 in cost savings per QALY lost. All options meet that test, and of these we need to choose the one with the highest net benefit (highest excess in value of cost savings minus value of lost QALYs). Strategy C, with a recall pattern of 2 years for aneurysms between 3.0 and 4.4 cm and 3 months for aneurysms between 4.5 and 5.4 cm, has the highest net benefit, and is the most cost-effective strategy. Increasing intervals beyond this does not provide sufficient additional cost savings to justify the additional QALY losses.

To summarise these figures as clearly as possible, our analysis suggests that the effect of changing from the current surveillance strategy to surveillance strategy C, the best of the options considered, would mean that the loss of value from the QALY gain per man invited would be equivalent to a loss of £1.24, but that the cost would be reduced by £2.57 per man invited, giving a net monetary benefit gain of £1.33.

Uncertainty and sensitivity

As was indicated in *Chapter 7*, in this particular case it is not feasible, given available data and analytical possibilities, to provide a robust, meaningful PSA that encompasses all the parameter and structural uncertainty. We have therefore focused on a more appropriate series of one-way sensitivity analyses. These are summarised in *Table 25*.

The first of these applies growth and rupture rates drawn from the three UK population-based screening studies that used internal aortic diameter measurements (as does the NAAASP), namely MASS, Gloucester and Chichester (see *Chapter 6*), and which could therefore be seen as most applicable to the UK programme. Strategy C clearly remains the preferred option and, although it is slightly less cost-effective than in the base case, the net benefit is still positive and substantial. As an alternative way to address the uncertainty around growth and rupture rates, the next sensitivity analyses reduce or increase growth rates by 10% and rupture rates by 30%. These ranges approximate one SD in the estimates of the value of the relevant parameter. Again, in each case, the preference for strategy C, over all other strategies, remains unchanged. Using an estimate of operative mortality rates from the NAAASP, similarly does not change the choice of strategy. Further sensitivity analyses consider the possibility that dropout rates (from recall) might be affected by different recall strategies but again the preference for strategy C is unaltered. Finally, we consider the effect of (arbitrarily) different relative costs for elective and emergency surgery and for the cost of rescanning. In no case does the choice of strategy change, although, not surprisingly, the magnitude of the cost savings from less frequent recall in strategy C (and hence its net benefit) are somewhat affected by the unit cost of rescans.

Discussion and conclusions

Long-term modelling of the implications of screening programmes is always difficult and typically involves unverifiable assumptions and estimates that have long-term implications. Screening for AAA is an unusual case in that we have been able to compare results from a long-term model initially based on 4-year data with 10 years of observation. The resultant problem was to identify a set of model parameters that would replicate the observed results at 10 years. We were able to do this imperfectly, but nevertheless can have more confidence in the recalibrated model than would otherwise have been appropriate with the original model. Then, with the systematic reviews and the RESCAN analyses of growth and rupture rates, we were able to go further in estimating the cost-effectiveness implications of alternative surveillance strategies.

TABLE 24 Adapted economic model cost-effectiveness results (30-year results) for alternative recall strategies

	Strategy A (1 year, 3 months)	Strategy B (2 years, 6 months)	ICER B compared with A	Strategy C (2 years, 3 months)	ICER C compared with A	Strategy D (1 year, 6 months)
Control arm						
Life-years	12.7157	12.7155		12.7157		12.7156
Cost (£)	271.65	260.23		265.87		265.46
Invited arm						
Life-years	12.7244	12.7240		12.7242		12.7241
Cost (£)	319.89	305.03		311.54		312.20
Difference						
Life-years	0.008659	0.008502	-0.0001578	0.008580	-0.00007983	0.008569
QALYS	0.006754	0.006631	-0.0001231	0.006692	-0.00006226	0.006683
Cost (£)	48.25	44.80	-3.45	45.68	-2.57	46.74
ICER £ per LY	5572	5270	21,853	5324	32,236	5454
ICER £ per QALY	7143	6756	28,016	6825	41,329	6993
Net benefit (λ=£20,000 per QALY)			0.99		1.33	

Costs based on 2010–11 prices – costs and mortality discounted at 3.5%. Survival based on deaths related to AAA deaths, accounting for other causes of death.

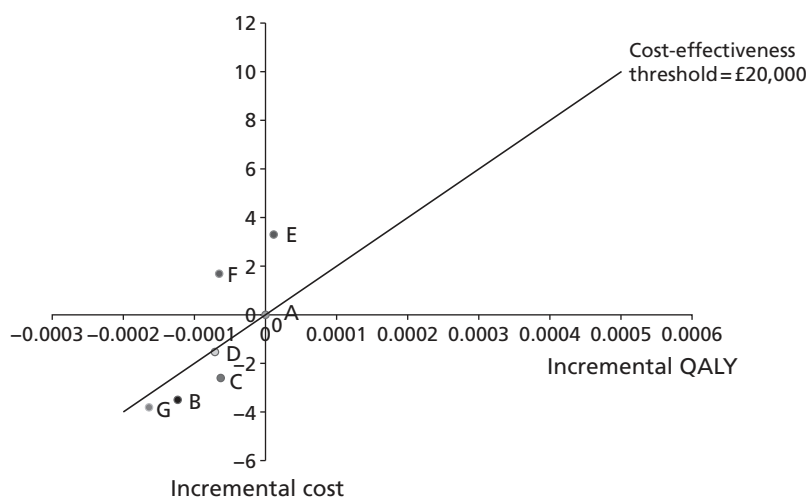


FIGURE 22 Cost-effectiveness plane for new screening interval strategies.

ICER D compared with A	Strategy E (6 months, 3 months)	ICER E compared with A	Strategy F (6 months, 6 months)	ICER F compared with A	Strategy G (3 years, 3 months)	ICER G compared with A
	12.7158		12.7156		12.7155	
	279.92		273.40		262.17	
	12.7244		12.7241		12.7240	
	331.49		323.35		306.64	
-0.00009086	0.008674	0.00001455	0.008576	-0.00008350	0.008449	-0.0002103
-0.00007087	0.006766	0.00001135	0.006689	-0.00006513	0.006590	-0.0001640
-1.51	51.57	3.32	49.95	1.70	44.47	-3.78
16,650	5945	228,111	5824	-20,365	5263	17,972
21,346	7622	292,450	7467	-26,109	6748	23,041
0.10		-3.09		-3.00		0.50

These show that from a cost-effectiveness perspective lengthening the surveillance interval for aneurysms of 4.5–5.4 cm reduces net monetary benefit and we have argued that decreasing that interval would not be practical. However, increasing the interval for recall of men with aneurysms between 3.0 and 4.4 cm from 1 year to 2 years improves cost-effectiveness, but increasing it further to 3 years worsens cost-effectiveness compared with 2 years and (marginally) compared with the current 1-year interval.

It is important to recognise that the absolute differences in outcomes and costs between the surveillance options we have considered are small, as are the absolute values of the net monetary benefit per man invited. They can be put into perspective by multiplying them up to reflect the impact on a large-scale screening programme. With a programme inviting around 260,000 men per year as will broadly be the situation when the NHS programme covers the whole of England,⁷³ the (present value of the) cost difference for the preferred option would be of the order of £660,000 per year, but the QALY loss would be equivalent to around 16 QALYs. Given the remaining uncertainties there has to be a question of whether or not the differences involved justify a change from the existing surveillance programme particularly as it would have to be explicit that this strategy was expected to be slightly inferior in terms of clinical effectiveness.

TABLE 25 Adapted economic model cost-effectiveness results (30-year results): sensitivity analyses of growth and ruptures rates, operative mortality rates, dropout rates, costs of surgery and cost of rescans. Incremental net benefit (INB) of each strategy is given compared with strategy A (1 year, 3 months)

	Strategy C (2 years, 3 months), INB (£)	Strategy B (2 years, 6 months), INB (£)	Strategy G (3 years, 3 months), INB (£)	Strategy D (1 year, 6 months), INB (£)	Strategy F (6 months, 6 months), INB (£)	Strategy E (6 months, 3 months), INB (£)
Base case	1.33	0.99	0.50	0.10	-3.00	-3.09
Growth and rupture rates from three UK population screening studies^{10,37,53} that used internal aortic diameter measurements						
Three UK screening studies	1.09	0.61	-0.11	-0.04	-3.01	-2.96
Growth rates						
Growth rates ↓10%	1.52	1.29	0.94	0.23	-2.95	-3.19
Growth rates ↑10%	1.13	0.68	0.03	-0.04	-3.05	-3.00
Rupture rates						
Rupture rates ↓30%	1.33	0.96	0.47	0.08	-3.02	-3.10
Rupture rates ↑30%	1.33	1.01	0.53	0.11	-2.99	-3.09
Operative mortality rate – base case^a 0.029 and 0.074						
0.024 (NAAASP)	1.36	1.16	0.58	0.25	-2.85	-3.10
Dropout rate from rescanning – base case 1.4%						
Dropout rate ↓20%	1.47	1.20	0.73	0.20	-3.06	-3.26
Dropout rate ↑20%	1.20	0.80	0.30	0.01	-2.95	-2.94
Costs of elective and emergency surgery – base case £19,985 and £12,806						
Elective ↑10%	1.38	1.07	0.63	0.14	-2.96	-3.10
Emergency ↓10%						
Elective ↑30%	1.47	1.25	0.88	0.24	-2.87	-3.12
Emergency ↓30%						
Elective ↓10%	1.28	0.90	0.37	0.05	-3.05	-3.08
Emergency ↑10%						
Elective ↓30%	1.18	0.72	0.11	-0.05	-3.13	-3.07
Emergency ↑30%						
Cost of rescanning – base case £68						
Cost of rescan ↓10%	1.10	0.69	0.20	-0.03	-2.81	-2.77
Cost of rescan ↓30%	0.64	0.11	-0.41	-0.28	-2.42	-2.11
Cost of rescan ↑10%	1.56	1.28	0.80	0.22	-3.20	-3.42
Cost of rescan ↑30%	2.02	1.87	1.41	0.47	-3.59	-4.07

↓, decreased by; ↑, increased by.

a In the base case, 0.029 relates to the mortality following surgery for screen-detected individuals, whereas 0.074 relates to those opportunistically detected. The data available from the NAAASP do not make a distinction.

Chapter 9 Discussion

In this chapter we discuss the results and interpretation of the two systematic literature reviews (see *Systematic review of small abdominal aortic aneurysm growth rates* and *Systematic review of small abdominal aortic aneurysm rupture rates*), the analyses of the IPD surveillance data sets (see *Analysis of individual patient data surveillance data sets*) and the patient factors influencing growth and rupture rates (see *Factors influencing growth and rupture rates*).

Systematic review of small abdominal aortic aneurysm growth rates

The methods and results of our systematic review are presented in *Chapters 3* and *4*. This is the first systematic review of small aneurysm growth rates since their inclusion in the earlier surgical management of aneurysms review of Hallin *et al.*,⁷⁶ which covered the literature from 1990 to 1997. Unlike this earlier study, which included only 816 patients from 13 different studies, we did not have to relax the eligibility criteria for studies (50 or more patients) and this allowed the identification of 15 suitable studies with 7630 persons for inclusion in a meta-analysis (see *Table 2*).

There are many reasons which might explain the large heterogeneity in growth rates between studies, particularly methodological and patient population issues. The methodological issues include the fact that patients have been entered into these studies since 1976, a 35-year time window during which the quality of aortic imaging has improved dramatically. Second, some recent studies have used imaging modalities other than US (such as CT) and it is known that there is poor agreement between CT and US aortic diameter measurements.^{77,78} Some studies have used both methods of imaging.^{22,29,32} However, a sensitivity analysis of studies that used only US imaging after 1990 was not associated with a reduction in heterogeneity. Third, aortic diameter has been measured in a variety of different planes, measurement cursors have been positioned on both the external and internal walls of the aorta (see *Table 2*) and only a minority of studies specified the standardisation of imaging protocol between observers (see *Table 3*). Fourth, growth rates have been estimated in a variety of different ways using (last–first diameter)/(time elapsed), linear regression or complex or multilevel modelling (see *Table 2*), and it has been reported that linear regression can overestimate aneurysm growth by up to 40% compared with multilevel modelling.¹³ Hierarchical modelling also resolves the problem of a small number of measurements possibly leading to exaggerated growth rates.¹³ There was evidence that some of the heterogeneity is explained by the use of linear regression and, in particular, (last – first diameter)/(time elapsed) to report aneurysm growth rates.

The patient population issues include ethnicity (which was reported rarely), the intervention policy of each study (which varied from aneurysm repair at 4.5 cm in the Huntingdon study to 6 cm in the Chichester study³⁴), the variable proportion of women in each study (which ranged from 0% in some studies to 24% in one Canadian study²⁹) and whether the aneurysm was identified by population screening or in hospital. During the period of patient recruitment to these studies, 1976–2005, there have been important improvements in medical therapy, with some studies reporting that use of statins slows the growth of aneurysms while ACE inhibitors may increase the growth of small aneurysms.^{31,79} Medical therapies, smoking and comorbidities were reported inconsistently across the 15 studies included in our review and frequently only at study entry; therefore, their influence on growth rates could not be evaluated (see *Table 2*).

Although this meta-analysis, based on the published literature, provides very strong evidence that growth rates increase markedly with aneurysm size, it only provides partial information about appropriate surveillance intervals for small aneurysms. The growth rate for a 3.5-cm aneurysm is estimated at 1.9 mm/year, whereas that for a 4.5-cm aneurysm is 3.5 mm/year, both rates being somewhat lower than those presented in the earlier review.⁷⁶ Given an exponentially increasing aneurysm diameter, as implied from the meta-regression in *Figure 4*, it would take on average 6.2 years for a 3.5-cm aneurysm to grow to 5.5 cm,

whereas a 4.5-cm aneurysm would take only 2.3 years. So surveillance intervals for a 4.5-cm aneurysm should be of the order of one-third of those for a 3.5-cm aneurysm. However, the meta-regression does not provide information about the variability of growth rates between individuals necessary to inform the choice of appropriate surveillance intervals.

Systematic review of small abdominal aortic aneurysm rupture rates

The methods and results of our systematic review were presented in *Chapters 3 and 4*. Rupture of an AAA is defined as blood leaking through the aortic wall into the peritoneal or retroperitoneal spaces; the diagnosis of rupture therefore depends on imaging (usually CT), findings at laparotomy or autopsy. A particular constellation of clinical symptoms including circulatory collapse, in the presence of a known aneurysm, also will give rise to the reporting of death from aneurysm rupture without autopsy. Contained or intramural rupture also may occur, when either the leak has sealed spontaneously or the bleeding remained intramural (the intramural blood from these ruptures usually can be detected by CT imaging). In contrast, abdominal or back pain and aortic tenderness in the presence of a known aneurysm does not necessarily imply rupture, although such aneurysms may be repaired urgently and listed as an emergency hospital admission. Very surprisingly, none of the eligible studies for this review reported their diagnostic criteria for aneurysm rupture and only 3^{22,23,41} of 14 studies reported the evidence from which a diagnosis of rupture was made. This lack of clarity about the diagnosis of rupture is a major limitation of these studies. In the European Society for Vascular Surgery Guidelines for the management of AAAs,⁸⁰ a clear definition of ruptured aneurysm is provided and hopefully this will be used in future studies: 'AAA rupture is defined as bleeding outside the adventitia of a dilated aortic wall. Rupture is further classified into free rupture in the peritoneal cavity and retroperitoneal rupture where the retroperitoneal tissues provide tamponade and reduce temporarily the volume of blood loss'.

Although many studies report the number of aneurysm ruptures, few studies have length of follow-up information to permit the estimation of rupture rates. Nevertheless, there are many more studies, with almost 10,000 patients, describing rupture rates of small aneurysms than were available for a recent systematic review of rupture rates in large aneurysms.²⁰ The latter, including only 533 patients in total, reported a rupture rate of 10.3 (95% CI 7.5 to 14.3) per 100 person-years for aneurysms 5.0–5.9 cm in diameter in those considered unfit for aneurysm repair.²⁰ The rupture rates reported here, for aneurysms of 3.0–5.5 cm in diameter, are much lower at 0–1.61 per 100 person-years, with a trend for rupture rates to increase with increasing diameter.

As no study reported the diagnostic criteria for rupture, the evidence from post-mortem studies was examined. There are limited data from post-mortem studies and because the post-mortem diameter is lower than any in vivo measurement, post-mortem data may be unreliable. A prospective autopsy series of 78 aneurysms where the autopsy aorta was subject to pressure inflation at 80–100 mmHg did not show any ruptures in specimens of ≤ 5.0 cm.⁸¹ This same study reported that without pressure inflation post-mortem diameters were usually smaller than any in vivo measurement, probably by 0.4–0.5 cm or in some cases by almost 50%. Therefore, data from the only large-scale autopsy series, which reported retrospectively on the rupture of aortic aneurysms in almost 24,000 consecutive autopsies at the Massachusetts General Hospital in the period 1952–75, are unreliable.⁸²

Both the PIVOTAL and CAESAR trials of endovascular repair compared with surveillance for small aneurysms reported in 2010 after the search for this review closed.^{51,83} In the PIVOTAL trial⁵¹ the rupture rate in the surveillance was 0.17 per 100 patient-years (although this includes some follow-up after aneurysm repair, which occurred in 31%). In the CAESAR trial,⁸³ although mean conditional follow-up was not reported, the rupture rate appears to be < 1 per 100 person-years. These are in keeping with the results reported here.

A new large prospective study based on population screening would be the most robust method of assessing the rupture rates of small aneurysms in the twenty-first century. Such a study would take time to set up and several years of follow-up before it could report. For now, an alternative way to assess the rupture rates of small aneurysms is through synthesis of a large amount of IPD from relevant studies. This is the strategy we pursued.

Analysis of individual patient data surveillance data sets

We presented our analysis of overall growth and rupture rates in men and women from 18 surveillance data sets in *Chapters 5* and *6*. Key results are shown in *Table 8*. This research has definitively quantified the extent to which AAA growth rates and risk of rupture increase with AAA diameter, to provide a scientific basis for selecting surveillance intervals for patients with small AAAs. For example, we have shown that the time taken for an AAA of ≤ 4.0 cm to have a 10% chance of growing to 5.5 cm is at least 3 years. For men with an AAA of ≤ 4.0 cm, it takes over 3.5 years to have a risk of rupture $> 1\%$.

These results are based on the largest collection of IPD made to date, and consistent methods of statistical analysis across multiple studies. Although three additional studies^{84–86} have been published up to September 2012, since the literature search that identified the studies for this meta-analysis was completed, one⁸⁴ had fewer than 100 patients, and another⁸⁵ appears to have considerable overlap with data already included in our analysis. The third study⁸⁶ includes 453 patients with 12 months of follow-up and would be unlikely to alter our findings which are based on 15,475 patients with longer follow-up.

Our findings have important implications for AAA surveillance programmes. As screening for AAA is becoming established in many countries there will soon be large cohorts of individuals under surveillance for AAAs. For example, the NAAASP provides yearly scans for 3.0–4.4-cm diameter AAAs and 3-monthly scans for 4.5–5.4-cm AAAs.⁹ The 95% confidence estimates for rupture risk from our study suggest that these surveillance intervals could safely be extended to 3 years for AAAs < 4.5 cm and yearly for 4.5–5.4-cm AAAs. The risk of rupture would be maintained at $< 1\%$, a figure that appears to be acceptable to patients with AAAs. This would reduce the average number of surveillance scans from approximately 22 to only 7 for a patient with a 3.0-cm AAA detected by screening. Even if the lower 95% prediction limits of our estimates are applied, to acknowledge that the populations in each study may have different growth and rupture rates, these surveillance intervals could be reduced to 2-yearly for 3.0–3.9-cm AAAs, yearly for 4.0–4.9-cm AAAs and 6-monthly for 5.0–5.4-cm AAAs. Using the same example as above, this would reduce the average number of surveillance scans required for a 3.0-cm AAA from approximately 22 to 10.

Most population-based screening programmes for AAA are focused on the elderly male population, aged ≥ 65 years. This study, which included 1743 women (11%), showed that overall there was no difference in aneurysm growth rates between men and women. Interestingly, when aneurysm growth rate was estimated using hierarchical modelling, allowing for accelerating growth rate with increasing aneurysm diameter, data from Tromsø no longer showed that growth rates were faster in women.³⁸ Only Edinburgh⁵⁴ and Leeds (Professor D Julian A Scott, personal communication) showed a significantly different growth rate in women. This underscores the heterogeneity observed both in this meta-analysis of the influence of sex and many other covariates and in previously published meta-analyses based on varied methods for estimating growth rate.^{19,87}

The fourfold higher rupture rate found for women compared with men is intriguing, particularly given that these data demonstrate that both sexes have similar growth rates. The sex imbalance in the risk of rupture has been identified in previous studies;⁴⁸ differences in anatomy, structure, sex steroids and smoking habits have all been suggested to play a role.⁸⁸ The clinical implication is that a lower AAA diameter threshold for surgery should be adopted for women, a recommendation already made by the joint council of the American Association for Vascular Surgery and Society for Vascular Surgery,⁸⁹ but one not yet supported by

randomised trial evidence. As the rupture rate for women with a 4.5-cm AAA is about the same as that for a man with a 5.5-cm AAA, a threshold for surgery of 4.5 cm might seem appropriate in women. However, the operative mortality and discharge outcomes appear to be worse in women than men. For instance, the US Medicare database shows that operative mortality after endovascular repair (now the majority procedure) is 3.2% in women compared with 1.8% in men, and similar findings have been reported in other studies.^{90–92} Therefore, competing risks must be carefully considered before amending guidelines or recommendations for intervention in women.

Despite the strong conclusions that can be drawn from this study, there remain some areas of uncertainty where future research efforts could be focused. The most obvious need is for further evidence for women with aneurysms in the diameter range 4.5–5.4 cm. Second, the substantial heterogeneity between studies we identified in growth and rupture rates could not be explained by adjustment for individual factors or study-level characteristics. If the underlying causes for these differences are biological rather than simply methodological, these may yield insights for developing interventions to lower growth rates in patients with small AAA; such treatments have been sadly lacking up to the present time.^{18,19} Such advances will only be possible through the analysis of large data sets, most likely to become available from surveillance within the national AAA screening programmes that are currently being set up. Third, recommended surveillance intervals may be lengthened in the future given the generally falling national rates of AAA rupture currently being experienced.^{48,93} Last, more research is needed on the acceptable risk to patients of exceeding 5.5 cm or rupture before the next scan. An alternative approach is to consider the cost-effectiveness of different surveillance policies. Decreasing surveillance frequency would reduce surveillance costs. However, it may also very slightly increase rupture rates, thereby decreasing overall life expectancy in AAA patients under surveillance and increasing the burden and cost of emergency surgery. Hence, we conducted a formal evaluation to identify which surveillance intervals for different sized AAAs would be most cost-effective, as reported in *Chapters 7 and 8*.

Factors influencing growth and rupture rates

Factors apart from sex that influence growth and rupture rates were systematically examined in the analysis of the IPD surveillance data sets (see *Chapters 5 and 6*). Aneurysm growth rates were consistently increased by about one-sixth in current smokers and decreased by about one-quarter in patients with diabetes. There was no evidence of any change in aneurysm growth rates over time and neither age, mean arterial pressure nor cardioprotective drugs, had a significant effect on growth rates. In contrast, small aneurysm rupture rates were doubled in current smokers, with age, mean arterial pressure and calendar year of enrolment being additional factors influencing rupture rates. These data suggest that the follow-up and management of the patient with small AAA could potentially be tailored to factors such as current smoking, diabetes and blood pressure, in addition to aneurysm diameter.

In every study, the growth rate of aneurysms in patients with diabetes was on average lower than in patients without diabetes, with no heterogeneity observed in the meta-analysis. Furthermore, the magnitude of the change in growth rate (approximately 25%) associated with diabetes was far greater than for any other covariate tested. This suggests that routine surveillance of small aneurysms might safely be less frequent in patients with diabetes. The biology of the aortic wall may be altered in diabetes with increased glycosylation, which together with other changes might underlie the reduced aneurysm growth rate in patients with diabetes. Most of these studies did not discriminate between type I and type II diabetes, although unpublished data from the United Kingdom Small Aneurysm Trial (UKSAT) suggest that most of the patients with diabetes (78%) were not taking insulin and in the Leeds study only type II diabetes was reported (Professor D Julian A Scott, personal communication). This might explain the trend for increased BMI to be associated with a reduced aneurysm growth rate in the unadjusted analysis. However, overall the patients with diabetes were few, concordant with the observation that diabetes is negatively associated with AAA.⁹⁴ As there were only four ruptures reported in patients with diabetes, it was not possible to reliably evaluate the influence of diabetes on aneurysm rupture.

Smoking was second only to diabetes in the magnitude of its effect on aneurysm growth but while the effect of current smoking on aneurysm growth was modest (~16%), current smoking doubled aneurysm rupture rates. The direction of the effect of smoking on aneurysm growth was consistent among all studies, except Leeds (Professor D Julian A Scott, personal communication). A limitation of our study, impacting on heterogeneity, is that non-smoking or ex-smoking status might have been defined differently in the different studies, particularly with respect to time from smoking cessation or very light tobacco usage.

The studies included in this meta-analysis span patients studied over a > 25-year period, since 1983. The prevalence of smoking has been decreasing since the mid-1970s and at the same time awareness of cardiovascular risk prevention in patients with small aneurysms has been increasing and the quality of US has improved dramatically. For these reasons, we explored whether or not the recruitment date of patients within each study (as a proxy for changing environmental, ultrasonographic and drug factors) might influence either aneurysm growth or rupture rates. Interestingly, although aneurysm growth rates appeared to be unchanged over time, rupture rates appeared to decrease. This is consistent with better control of hypertension (higher mean arterial pressure increases rupture rates) and lower prevalence of smoking as well as with the decreasing incidence of aneurysm rupture, which is being reported from several different countries.^{95–97} The contrasting effects of enrolment date on growth and rupture rates also may indicate that although cardioprotective drugs might influence rupture rates they are unlikely to have any strong influence on aneurysm growth.

Individually, none of the cardioprotective drugs (lipid-lowering drugs, aspirin, beta blockers, calcium channel blockers or ACE inhibitors) showed significant associations with aneurysm growth, and the magnitude of any individual effect was very small (about 0.2 mm/year for statins and 0.1 mm/year for other drugs). One of the included studies was a formal evaluation of the effect of propranolol on aneurysm growth rate in about 500 patients.⁴⁰ Based on the findings reported here, this trial was very underpowered and trials of approximately 3700 patients would be necessary to show a reduction in aneurysm growth rates of 0.2 mm/year at 80% power, assuming growth rates have a SD 2.2 mm/year. The findings reported here for lipid-lowering drugs are consistent with other meta-analyses showing a possible association between statin usage and slower aneurysm growth rate.^{18,19,98} The finding that ACE inhibitors increased growth rates in the UKSAT⁷⁹ was not substantiated by other studies. Particularly in the older studies, few of the patients included in the current meta-analysis were taking cardioprotective medications and even if patients were taking these drugs at baseline, there is no evidence about continued patient compliance with medication. This is pertinent since both of the randomised trials assessing the effect of beta blockers on aneurysm growth illustrated the poor compliance with these drugs in patients with small aneurysms.^{40,99}

This individual patient meta-analysis of the influence of demographic factors and drugs on small aneurysm growth and rupture rates overcomes a number of limitations found in meta-analyses of published data.^{18,19,87,100} First, data are strictly limited to the aneurysm diameter size range of 3.0–5.5 cm, the range which is relevant to most population screening programmes. Second, the study uses a single statistical method of estimating aneurysm growth rates, to overcome some of the heterogeneity associated with using different methods of growth rate estimation, particularly the use of (last–first diameter)/(time elapsed). Third, through application of an adjustment for overestimation of diameters using CT scans compared with ultrasonography, studies using both CT and US data could be included. Fourth, as rupture is a rare event in small aneurysms, there is an opportunity to study important factors, other than aortic diameter, which may influence rupture rates and alter patient management.

Chapter 10 Conclusions

Clinical and policy conclusions

In our systematic reviews of the growth and rupture rates of small AAA we primarily identified that both of these outcomes were related to AAA size, with larger AAA having higher rates of growth and higher rates of rupture. We estimated that the average time for a 3-cm AAA to grow to 5.5 cm is 9.6 years and for a 5-cm AAA is 1.1 years. We were unable to provide the same size-based estimates for risk of rupture from our systematic review since the data informing such an analysis were insufficient. We can only conclude that the rupture rate of small AAAs (3.0–5.5 cm in diameter) appears to lie between 0 and 1.61 per 100 person-years.

In order to address the deficiencies of the systematic reviews we went on to obtain IPD for 15,475 patients in AAA surveillance programmes. We harmonised and combined the data from these individual patients to obtain estimates of AAA growth and rupture rates. As expected, we identified that AAA growth and rupture rates were related to AAA size. In this analysis we determined outcomes for men and women separately. For men with a 3.0-cm AAA, the time taken to have a 10% chance of exceeding 5.5 cm was 7.4 years, and for a 5.0-cm AAA the time was 0.7 years. For women these times were 6.9 years and 0.7 years. We also assessed the time for small AAAs to exceed a 1% per annum rupture risk. In men with 3.0-cm and 5.0-cm AAAs these times were 9.3 years and 1.4 years, respectively. The times for women were 3.5 years and 0.7 years. These data highlight the sex difference in AAA rupture rates, with women more likely to rupture at lower AAA sizes than men, suggesting that the threshold for surgical intervention in women should be lower than in men.

From our analysis of IPD we identified that smoking was independently associated with both accelerated AAA growth and the risk of AAA rupture. Although all patients with AAA are routinely offered smoking cessation therapy in the majority of clinical practices, this finding underlines the importance of instituting measures to reduce tobacco consumption among patients with AAA and provides the most robust evidence to date with which to counsel patients. This information is also of importance to the non-specialist NHS practitioner, as the majority of patients with small AAAs will be managed in surveillance programmes with little or no physician contact.

Although we identified that higher mean arterial pressure was associated with a higher risk of AAA rupture, we were unable to demonstrate an effect of antihypertensive drugs. The appropriate use of antihypertensive medications, with targets of 130/80 mmHg, is nevertheless important in AAA patients. Although this strategy will require further investigation to determine any effect on rupture rates, the expected benefits in terms of overall cardiovascular mortality reduction justify its recommendation.

Our study has implications for surveillance strategies. From our IPD meta-analysis, we have demonstrated that most of the smallest AAAs will remain quiescent over many years. This suggests that current surveillance strategies for small AAAs could be refined to reduce the number and frequency of surveillance scans required and therefore the costs associated with AAA surveillance.

In theory the individual characteristics that influence growth or rupture rates, such as smoking and diabetes, could be taken into account to tailor surveillance intervals for each individual. However, the effects of such variables are not substantial enough to justify the organisational difficulty that such personalised surveillance strategies would involve, despite the desire for this from patients. Similarly, AAA measurements before the current one are informative about a person's rate of AAA growth¹⁷ and could, in principle, also be taken into account.

Our cost-effectiveness investigations showed that lengthening the surveillance intervals from 1 year for 3.0–4.4-cm AAAs was cost-effective, whereas lengthening the 3-month interval for 4.5–5.4-cm AAAs was neutral with respect to cost-effectiveness. However, the differences in costs were small, up to about £4 within an overall cost of £300 per man invited to AAA screening. Also our results may be susceptible to the detailed modelling assumptions made and parameter estimates used, and the fact that our updated health economic model did not validate very well on the 10-year MASS trial data. Nevertheless, the cost-effectiveness analyses support the lengthening of surveillance intervals for the smallest aneurysms, in line with our clinical conclusions.

Research implications

From the work we have undertaken, we draw a number of conclusions about future research priorities, as follows.

We identified that the definition and diagnostic criteria of AAA rupture were poorly reported in published studies. There is a need for standardised definitions and reporting, so that rupture rates can be more reliably estimated. One major hurdle to overcome is the determination of whether or not AAA rupture is reported accurately in mortality statistics. Many sudden deaths, particularly in elderly populations who are at the highest risk of AAA rupture, are likely to be recorded on death certificates as due to cardiac or cerebrovascular causes, missing many cases of AAA rupture. Declining post-mortem examination rates will contribute to the potential under-reporting of AAA-related mortality.

We demonstrated that surveillance intervals for most small aneurysms can be extended safely, with such extension being cost-effective for the smallest aneurysms. These recommendations are based on opinions from a single patient focus group rather than a more widespread patient preference study. Given the current knowledge, there is a need to investigate patient preferences concerning extending surveillance intervals, especially in the upper half of the small aneurysm diameter range where such extension could be clinically acceptable but without cost-effectiveness benefit.

We have determined that hierarchical modelling provides a methodologically appropriate framework for analysing data on AAA growth rates and recommend that this method be used in future studies.

Based on the observation of growth rates in patients with 3.0-cm diameter aneurysms, modelling could be conducted to indicate appropriate recall intervals for men identified as having an aortic diameter of 2.5–2.9 cm at initial aneurysm screening visit.

We observed large variation in growth rates between studies, which was largely unexplained. The identification of both methodological reasons, for example how AAA diameters are measured, and biological causes for this variation are important. The latter could lead to the identification of factors and biological pathways related to increased growth rates or rupture rates that were amenable to intervention. Such interventions might then be assessed in randomised trials.

We have shown that the clinical progression of an AAA is different in women compared with men, with women at substantially higher risk of rupture. Currently women are not screened for AAAs in the UK, and those with opportunistically detected AAAs are usually entered into generic rather than sex-specific surveillance programmes. In addition to obtaining evidence to investigate the efficacy and cost-effectiveness of AAA screening in women, surveillance programmes and criteria for considering surgery need to be tailored for women. Formal evaluation of a lower intervention threshold for women, either via a randomised trial or modelling studies, is a research priority.

We have shown that increasing mean arterial blood pressure increases the risk of aneurysm rupture. There is a need to formally evaluate whether or not reducing blood pressure to $\leq 130/80$ mmHg would reduce the

risk of rupture, in both small aneurysms managed in surveillance programmes and in high-risk patients with larger aneurysms who, as part of the National Quality Improvement Programme, are being turned down for elective aneurysm repair in increasing numbers.

The findings that age, sex and blood pressure appear to have strong associations with aneurysm rupture but not aneurysm growth are intriguing and hint at the presence of differential mechanisms promoting aneurysm growth and aneurysm rupture. The association of diabetes with retarded AAA growth rates reiterates the intriguing negative association between diabetes and AAA prevalence and further exploration of the mechanistic pathways leading to diabetes may provide insights into the pathogenesis of AAA.

Although we have provided evidence about appropriate surveillance intervals for small AAAs, we have always used the currently accepted diameter of 5.5 cm for considering elective surgery. Related research could aim to determine whether it is possible to develop personalised criteria or patient-specific thresholds for elective surgery.

Comparable studies with substantial patient numbers are required for the kind of research undertaken here. Future research should focus on the collection and use of large, well-structured and internationally compatible data sets, along with statistical and epidemiological methods needed for their harmonisation and analysis. For example, work is required to determine how to combine data based on different methods of AAA size measurement. The recent inception of national AAA screening programmes in several countries may facilitate such research.

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Contributions of authors

SG Thompson was principal investigator of the project and the RESCAN Collaboration, provided overall direction and overview, supervised the statistical analyses, and collated and revised material for this report.

LC Brown undertook data extraction and evaluation of published studies in the systematic reviews, collated and harmonised the IPD surveillance data sets acquired from the RESCAN collaborators, and edited this report.

MJ Sweeting undertook statistical analyses for the systematic reviews, developed the statistical modelling framework for growth and rupture in the IPD data sets to inform surveillance intervals, and provided information from these analyses in a form suitable for the health economic analyses.

MJ Bown organised the patient focus group, collaborated on the analyses of the IPD surveillance data sets, and provided clinical input into the RESCAN Collaboration.

LG Kim undertook reanalyses of the MASS trial data and provided input into developing the health economic modelling framework.

MJ Glover developed the health economic modelling framework and undertook the cost-effectiveness analyses.

MJ Buxton supervised the health economic modelling work and drafted the conclusions from the cost-effectiveness analyses.

JT Powell directed the systematic reviews, invited investigators to participate in the RESCAN Collaboration, provided epidemiological and biological input for the analyses of growth and rupture rates, and led the drafting of a number of the resulting published papers.

All authors provided comments on a draft version of this report.

Other contributions

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Appendix 1 Protocol, search strategy and list of excluded studies for systematic review of growth of small abdominal aortic aneurysms

1.0 Protocol

1.1 Introduction

From spring 2009, the UK National aneurysm-screening programme has been slowly launched across England. The programme uses ultrasonography to detect and measure the diameter of abdominal aortic aneurysms (AAAs) to reduce the number of deaths. However, the programme still needs clear policies for their intervention and surveillance protocols. The policies, which are currently under development, will in large depend on the growth rate (GR) and rupture rate of aneurysms. At present, large aneurysms (over 5.5 cm in diameter) are referred to elective surgery (open surgery or endovascular aneurysm repair, EVAR), while optimal management of small aneurysms (less than 5.5 cm in diameter), which represents ca. 90 per cent of all screen-detected AAAs,¹ seems to be in favour of surveillance.²⁻⁵

A number of studies have reported on growth rates of small aneurysms and recommended the following frequencies of follow-up examinations (*Table 1*). The reported growth rates of small aneurysms (3.0 cm to 3.9 cm in aortic diameter) ranged from 0.2 to 0.41 cm per year,^{6,7} while Santilli *et al.* reported a lower rate of 0.11 cm per year.⁸ In many cases, simple linear regression has been used to estimate growth rates. However, this does not take into account that aneurysmal growth rate may accelerate with an increased diameter.⁹ In addition, it has been reported that aneurysm growth is faster in smokers and slower in patients with diabetes, while differences between genders are still unclear.⁹⁻¹³ There have been several trials, using antibiotics and beta blockers, to reduce AAA growth (*Table 2*). None of these trials provide persuasive evidence that a treatment to slow aneurysm growth has been identified, but they should provide good quality data for aneurysm growth.

Most of these studies of aneurysm diameter surveillance have used ultrasonography for monitoring. A few studies have used CT scanning³ or a mixture of CT scanning and ultrasonography. In some comparative studies, the measurements recorded by CT scanning were different to those recorded by ultrasonography.¹⁴⁻¹⁶ This observation will have to be accounted for in the systematic review and meta-analyses proposed. Therefore, it will be useful to assess the mean difference between ultrasonographic and CT diameter measurements to inform the analysis of this systematic review.

This systematic review will be made up of three elements, i.e. literature searching, summary of data, and meta-analysis (*Figure 1*). Studies will also be identified for an individual patient data (IPD) meta-analysis. The published data on GR for small AAA has not yet been synthesized nor has safe surveillance intervals been determined, especially in women. Therefore, further to the systematic review we will aim to re-analyse all the available individual patient data to achieve more precise estimates of growth rates and determine probabilities of growth within different ranges of aortic diameter. This, in turn, will have an impact on the re-screening intervals for patients with small AAAs.

1.2 Specific Aims

The aims of this study are to systematically review published and unpublished data of growth rates of small AAA, as measured by ultrasound or a computed tomography (CT) scan.

We will focus on the following question:

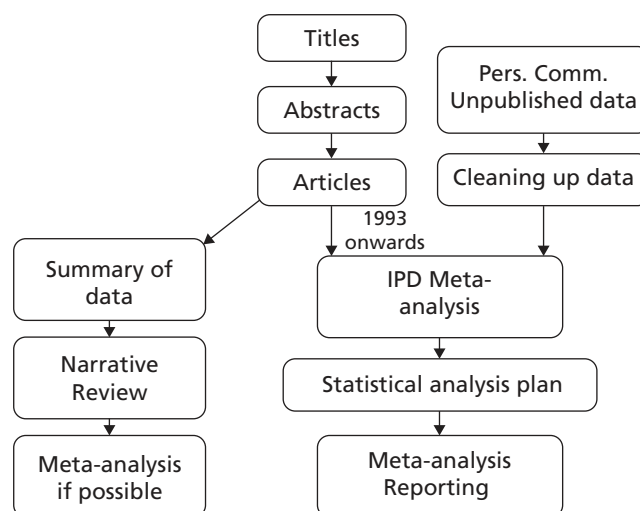
- What are the growth rates of small AAAs?

TABLE 1 Summary of follow-up data of small abdominal aortic aneurysms

Author	Aortic diameter	Follow-up	Additional info
Santilli <i>et al.</i> , 2002 ⁸	3.0cm to 3.9cm	After 3 years	Male patients
McCarthy <i>et al.</i> , 2003 ¹⁷	3.0cm to 3.4cm	At 3 years	n/a
Lindholt <i>et al.</i> , 2000 ⁶	3.0cm to 3.5cm	At 3 years	n/a
Lindholt <i>et al.</i> , 2000 ⁶	3.5cm to 3.9cm	Every other year	n/a
McCarthy <i>et al.</i> , 2003 ¹⁷	3.5cm to 3.9cm	At 1 year	n/a
Lindholt <i>et al.</i> , 2000 ⁶	4.0cm	Every year	n/a

TABLE 2 Selection of trials to reduce AAA growth (antibiotics and beta blockers)

Author	Agent	Aortic expansion rate
Mosorin <i>et al.</i> , 2001 ¹⁸	Doxycycline	Doxycycline may positively change the outcome of patients with small AAA.
Vammen <i>et al.</i> , 2001 ¹⁹	Roxithromycin	Roxithromycin reduced the expansion rate of AAAs, in comparison to placebo.
Baxter <i>et al.</i> , 2002 ²⁰	Doxycycline	Doxycycline is linked with a gradual reduction in plasma MMP-9 levels. Additional studies are needed to determine effects of doxycycline on aneurysm growth.
Karlsson <i>et al.</i> , 2009 ²¹	Azithromycin	Azithromycin had no effect on AAA expansion.
Propranolol Aneurysm Trial Investigators, 2002 ²²	Propranolol	The agent did not significantly affect growth rate of small AAAs.
Lindholt <i>et al.</i> , 1999 ²³	Propranolol	Only 22% of small AAA was treatable with propranolol (40 mg twice a day) for two years, in comparison to placebo. Need large-scale studies.

**FIGURE 1** An outline of the strategy behind the systematic review.

We are also interested in two related questions:

- Given a particular aneurysm diameter, what is the probability of the aneurysm growth at specified time points (3 months, 6 months, or twelve months)?
- Which factors (size, statins, etc.) influence growth rates?

1.3 Methods

Narrative review

This protocol will be approved by a review committee in order to answer the above questions and the protocol will be followed rigorously by the systematic reviewers (JTP, SMG). A systematic search of the literature will be performed. Search strategies will be designed for MEDLINE, EMBASE and CENTRAL using a combination of controlled vocabulary (MeSH or Emtree) terms and free text terms. Clinicaltrials.gov (<http://clinicaltrials.gov>), Current Controlled Trials (<http://www.controlled-trials.com/>) and the National Research Register (UK) will also be searched for details of ongoing or unpublished trials. All articles between 1950 (MEDLINE) or 1980 (EMBASE) and up until 2009, which matched the inclusion and exclusion criteria (see below), will be selected for the systematic review.

Other sources of information will also be searched:

- Reference lists of published key articles
- Books and conference notes.
- Key authors will be contacted to identify additional sources of publications/data.

The restriction on language of publications applies to English, German, French, Swedish, Danish, and Norwegian.

IPD meta-analysis review

Same as above, except for the following:

All articles between 1993 (MEDLINE) or 1993 (EMBASE) and up until the end of 2009, which matched the inclusion and exclusion criteria (see below), will be selected for the IPD meta-analysis. The IPD reviews will be limited by data availability and age of study (e.g. a 15 year cut off for paper inclusion because older papers are unlikely to provide us with IPD information).

1.4 Study Selection

The exclusion criteria (see below) will be applied to all the accumulated sources of information, such as peer-reviewed articles, conference notes, books, and unpublished data. The initial rejection or inclusion will be based on the study title. However, if the study title is obscure, the abstract will be reviewed. In cases where abstracts are unavailable or inconclusive, the full article will be acquired and reviewed.

Exclusion criteria:

- Review articles.
- Editorials.
- Letters.
- Case reports.
- Studies where patient data have been duplicated.
- Non-human studies (animal, in-vitro, post-mortem).
- Less than 100 patients.

Full text-versions of the selected shortlist of documents will be obtained. The two reviewers (JTP, SMG) will individually assess them to make sure that they adhere to the initial eligibility criteria. The two reviewers will

then individually select studies that meet the inclusion criteria (see below). If an agreement cannot be reached, a third author (LCB) will cast the deciding vote.

The inclusion criteria will be as follows:

- Men or women ≥ 50 years of age.
- All ethnic groups.
- Studies must include participants with a baseline infrarenal AAA (from 3.0 to < 6.0 cm in diameter).
- Studies must include 500-patient years of observation for small aneurysms (IPD).
- For studies reporting duplicated patient data, the most recent or most comprehensive publication will be included.
- Serial ultrasound or CT scans (with size assessed on at least two occasions separated by at least 6 months).

We will focus on retrieving additional information from studies with more than 500-patient years. All studies will be included in the narrative review.

1.5 Data Extraction and Quality Scoring

A data extraction form or a scoring system, which identifies technical details, patient characteristics and potential biases etc., in the selected documents, will be designed independently by the reviewers (JTP, SMG). Any disagreement will be resolved by a third person (LCB). The results of the checklist will be summarised for each study and any study publication that fails to provide sufficient details will be either rejected or the study authors will be contacted for completion of the checklist. The demographic details (age, gender, ethnicity, cigarette smoking status) will also be described. Any study in which authors who does not respond to the reviewer's repeated correspondence for essential information will be withdrawn from the selected shortlist of documents.

Criteria for quality control are as follows:

- Prospective/retrospective.
- Source: population screening versus hospital.
- Consecutive patients entered.
- Defined surveillance policy.
- Defined intervention policy.
- Description of outcomes how growth was ascertained, points of censorship (e.g. rupture, aneurysm repair and death) and how the study was evaluated (multiple, blinded, observation).
- Reporting methods: graphic, descriptive, tables, statistical uncertainty.

Other data to be extracted:

- Heterogeneity (men versus women; chronological time; country).
- Description of baseline characteristics (specifically; age, sex, ethnicity, smoking status, diabetes).

1.6 Data synthesis and analysis

Narrative review

The data synthesis will summarise the extracted data of the included and eligible studies. All the relevant information (e.g. intervention, population, outcomes) will be tabulated. The ineligible studies will also be tabulated (giving reasons for exclusion).

Studies will present their results in many different ways, and so a semi-quantitative review is the most feasible option. For example, some studies present mean growth rate whilst others present the probability of

exceeding a certain threshold within a specified time period. The nature in which the outcome is reported together with the statistical analysis used to calculate growth rates will be tabulated for each study.

If feasible, an estimate of the average growth rate (mm/year) together with its standard error will be extracted from each study. Where 95% confidence intervals are quoted in place of standard errors, these will be converted by assuming normality and using the formula $SE = (UCL - LCL) / 3.92$, where UCL and LCL are the upper and lower limits of the 95% confidence interval.²⁴

If a sample standard deviation and the number of patients is quoted then this will be converted to a standard error of the mean using the formula $SE = SD / \sqrt{n}$. If a 95% reference range is quoted, then this will first be converted to a standard deviation using the formula $SD = (URR - LRR) / 3.92$, where URR and LRR are the upper and lower limits of the 95% reference range, and then to a standard error of the mean as above.

A random-effects meta-analysis will be conducted on the rate scale (or on the log rate scale with standard errors transformed using the delta method) using the method of DerSimonian and Laird.²⁵ Heterogeneity will be assessed using the I^2 statistic. Further exploration of between study heterogeneity will be investigated using meta-regression, for example using the mean baseline diameter as a study level covariate. Results will be presented with forest plots, and small study/ publication bias investigated using funnel plots.

IPD review

For studies that provide individual patient data the analysis of growth rates will proceed as follows. Linear random-effects models will be fit to the IPD data allowing for a random baseline diameter and growth rate for each individual in a study. To synthesise the evidence, if feasible, a three-level hierarchical model will be used, with levels for study, individual, and observation. The mean pooled growth rate can be estimated and predictions about the probability of crossing the 55 mm threshold can be made for a number of baseline diameters at different time points following screening. If a three-level model is not feasible then a two-stage approach will be implemented where the estimated mean baseline diameter and growth rate from each study will be synthesised using a bivariate meta-analysis to allow for the correlated outcomes.

Variables that may affect growth rates will be investigated by entering them into the growth model as covariates. However, such analyses may be considered secondary since covariate information will not be available from all studies.

2.0 Search strategy for systematic review of growth rates of small abdominal aortic aneurysms

Database: Ovid MEDLINE(R) <1950 to September Week 4 2009>

Search Strategy:

1. Aortic Aneurysm, Abdominal/ (9934)
2. Aortic Rupture/ (6705)
3. ((abdominal or aort\$) adj5 aneurysm?).ti,ab. (21792)
4. AAA.ti,ab. (5659)
5. or/1-4 (29273)
6. di.fs. (1607182)
7. ra.fs. (507926)
8. us.fs. (148151)
9. or/6-8 (2132304)
10. exp Ultrasonography/ (198667)
11. Mass Screening/ (65350)
12. Aortography/ (9130)
13. Angiography/ (48487)
14. exp Tomography/ (450036)

15. (survei\$ or screen\$ re-screen\$ or rescreen\$ or monitor\$ or scan\$ or ultrasound or ultra-sound or CT or angiography or ultrasonograph\$.ti,ab. (919931)
16. or/10-15 (1401499)
17. 5 and (9 or 16) (13876)
18. (grow\$ or expan\$ or diameter? or ruptur\$ or size?).ti,ab. (1556989)
19. 17 and 18 (5589)

Database: EMBASE <1980 to 2009 Week 51>

Search Strategy:

1. exp abdominal aorta aneurysm/ (9971)
2. exp aorta rupture/ (2109)
3. exp aneurysm rupture/ (6116)
4. ((abdominal or aort\$) adj5 aneurysm?).ti,ab. (16134)
5. or/1-4 (23719)
6. di.fs. (1441356)
7. dm.fs. (92679)
8. exp echography/ (252641)
9. screening/ or mass screening/ (47280)
10. disease surveillance/ (2250)
11. exp angiography/ (139893)
12. exp tomography/ (344103)
13. ultrasound/ (40545)
14. (survei\$ or screen\$ or re-screen\$ or rescreen\$ or monitor\$ or scan\$ or ultrasound or ultra-sound or CT or angiography or ultrasonograph\$.ti,ab. (1029589)
15. or/6-14 (2426670)
16. 5 and 15 (13915)
17. (grow\$ or expan\$ or diameter? or ruptur\$ or size?).ti,ab. (1264858)
18. 16 and 17 (6819)

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#1	MeSH descriptor Aortic Aneurysm, Abdominal explode all trees	499
#2	MeSH descriptor Aortic Rupture explode all trees	83
#3	((abdominal or aort*) near aneurysm*)	872
#4	(AAA)	327
#5	(#1 OR #2 OR #3 OR #4)	984
#6	MeSH descriptor Ultrasonography explode all trees	5740
#7	MeSH descriptor Mass Screening explode all trees	4314
#8	MeSH descriptor Aortography explode all trees	94
#9	MeSH descriptor Angiography explode all trees	4680
#10	MeSH descriptor Tomography explode all trees	7584
#11	(survei* or screen* re-screen* or rescreen* or monitor* or scan* or ultrasound or ultra-sound or CT or angiography or ultrasonograph*)	81185
#12	(#6 OR #7 OR #8 OR #9 OR #10 OR #11)	89654
#13	(grow* or expan* or diameter* or ruptur* or size*)	51035
#14	(#5 AND #12)	377
#15	(#13 AND #14)	190

Clinical Trials Registers

ClinicalTrials.gov and Current Controlled Trials – search term “abdominal aortic aneurysm” or AAA.

3.0 List of studies excluded from systematic review of growth rate of small abdominal aortic aneurysms

Study	Title	First author	Journal/Year	Reasons for exclusion
(1)	AAA in high-risk patients. Outcome of selective management based on size and expansion rate.	Bernstein, E.F.	<i>Ann Surg</i> 1984	3
(2)	Actuarial analysis of variables associated with rupture of small AAAs.	Cronenwett, J.L.	<i>Surgery</i> 1985	3, 7
(3)	How Fast do Very Small AAAs Grow.	Collin, J.	<i>Eur J Vasc Surg</i> 1989	2, 3, 7
(4)	Prognosis of AAAs. A population-Based Study.	Nevitt, M.P.	<i>N Engl J Med</i> 1989	3
(5)	Wachstumskurven von Bauchortenaneurysmen.	Kremer, H.	<i>Bildgebung/ Imaging</i> 1989	1, 2
(6)	The Natural History of Small AAAs: an US study.	Walsh, A.K.M.	<i>Eur J Vasc Surg</i> 1990	3, 7
(7)	Natural History of Patients with AAA.	Glimaker, H.	<i>Eur J Vasc Surg</i> 1991	3, 4
(8)	Growth rates of subclinical AAAs – implications for review and rescreening programmes.	Collin, J.	<i>Eur J Vasc Surg</i> 1991	3
(9)	The Natural History of AAAs.	Guirguis, E.M.	<i>Am J Surg</i> 1991	3, 7
(10)	Determination of the expansion rate and incidence of rupture of AAA.	Limet, R.	<i>J Vasc Surg</i> 1991	3, 6
(11)	The Spontaneous Course of Small AAAs. Aneurysmal Growth Rates and Life Expectancy.	Zollner, Z.	<i>Klin Wochenschr</i> 1991	7
(12)	Aortic Aneurysms: Growth Rates Measured with CT.	Hirose, Y.	<i>Radiology</i> 1992	8
(13)	The selective management of small AAA: The Kingston Study.	Brown, P.M.	<i>J Vasc Surg</i> 1992	2
(14)	Expansion pattern and risk of rupture of AAA that were not operated on.	Bengtsson, H.	<i>Eur J Surg</i> 1993	3, 7
(15)	Morphology of small aneurysms: definition and impact on risk of rupture.	Faggioli, G.L.	<i>Am J Surg</i> 1994	3, 4
(16)	A statistical analysis of the growth of small AAAs.	Grimshaw, G.M.	<i>Eur J Vasc Surg</i> 1994	3, 4
(17)	Screening for AAA.	Law, M.R.	<i>J Vasc Surg</i> 1994	9
(18)	AAA expansion rate: Effect of size and beta-adrenergic blockade.	Gadowski, G.R.	<i>J Vasc Surg</i> 1994	3, 5, 6
(19)	Selective management of AAAs in a prospective measurement program.	Brown, P.M.	<i>J Vasc Surg</i> 1996	2
(20)	A prospective study to define the optimum rescreening interval for small AAA.	Cook, T.A.	<i>CardiovascSurg</i> 1996	2, 4
(21)	Growth Rate of Infrarenal Aortic Aneurysms.	Stonebridge, P.A.	<i>Eur J Vasc Endovasc Surg</i> 1996	2
(22)	What is the Long-term Outcome for Patients With Very Small AAAs.	Watson, C.J.E.	<i>Eur J Vasc Endovasc Surg</i> 1997	3, 7

Study	Title	First author	Journal/Year	Reasons for exclusion
(23)	Expansion rates of small AAAs.	Englund, R.	<i>Aust N Z J Surg</i> 1998	6, 7
(24)	Mortality results for randomised controlled trials of early elective surgery or ultrasonographic surveillance for small AAAs.	UK Small Aneurysm Trial Participants	<i>Lancet</i> 1998	2
(25)	AAA Wall Mechanics and their relation to Risk of Rupture.	Sonesson, B.	<i>Eur J Vasc Endovasc Surg</i> 1999	4, 7
(26)	The relationship between AAA wall compliance, maximum diameter and growth rate.	Wilson, K.	<i>Cardiovasc Surg</i> 1999	2, 3
(27)	Watchful waiting in cases of small AAAs - appropriate for all patients?	Valentine, R.J.	<i>J Vasc Surg</i> 2000	3, 4
(28)	Optimal interval screening and observation of AAAs.	Lindholt, J.S.	<i>Ugeskr Laeger</i> 2001	2
(29)	The incidence of Small AAAs and the Change in Normal Infrarenal Aortic Diameter: Implications for Screening.	Wilmink, A.B.M.	<i>Eur J Vasc Endovasc Surg</i> 2001	2, 4
(30)	Are antihypertensive drugs associated with AAAs?	Wilmink, A.B.M.	<i>J Vasc Surg</i> 2002	2, 4
(31)	Growth rate of AAAs. Ultrasounds study and clinical outcome.	Simoni, G.	<i>Minerva Cardioangiol</i> 2002	1
(32)	Follow-up of small aneurysms in the infrarenal abdominal aorta.	Barba-Vellez, A.	<i>Angiologia</i> 2002	2
(33)	Ten-year outcome of patients with small AAA.	Biancari, F.	<i>Am J Surg</i> 2002	3, 6, 7
(34)	Long-term outcomes of immediate repair compared with surveillance of small AAAs.	UK Small Aneurysm Trial Participants	<i>N Engl J Med</i> 2002	2
(35)	Prediction of rupture risk in AAA during observation: wall stress versus diameter.	Fillinger, M.F.	<i>J Vasc Surg</i> 2003	4
(36)	Discontinuous, Staccato Growth of AAAs.	Kurvers, H.	<i>J Am Coll Surg</i> 2004	3, 6
(37)	Four-year follow up of patients with untreated AAAs.	Aziz, M.	<i>ANZ J Surg</i> 2004	4
(38)	Mortality and Size of AAA at Long-Term Follow-Up of Patients Not Treated Surgically and Treated With or Without Statins.	Sukhija, R.	<i>Am J Cardiol</i> 2006	4, 6, 7
(39)	Influence of sex on expansion rate of AAAs.	Mofidi, R.	<i>Br J Surg</i> 2007	4, 7
(40)	Optimizing compliance, efficiency, and safety during surveillance of small AAAs.	Armstrong, P.A.	<i>J Vasc Surg</i> 2007	4
(41)	Hyperhomocysteinaemia is Associated with the Rate of AAA Expansion.	Halazun, K.J.	<i>Eur J Vasc Endovasc Surg</i> 2007	6
(42)	Ultrasound surveillance of ectatic abdominal aortas.	Devaraj, S.	<i>Ann R Coll Surg Engl</i> 2008	7
(43)	Activated protein C-protein C inhibitor complex: A new biological marker for aortic aneurysms.	Kolbel, T.	<i>J Vasc Surg</i> 2008	4, 6
(44)	The use of statins and fate of small abdominal aortic aneurysms.	Mosorin, M.	<i>ICVTS</i> 2008	5, 6

Study	Title	First author	Journal/Year	Reasons for exclusion
(45)	Search for Serum Biomarkers Associated with AAA growth - A Pilot Study.	Vega de Ceniga, M.	<i>Eur J Vasc Endo</i> 2009	2, 3
(46)	The PIVOTAL study: A randomized comparison of endovascular repair versus surveillance in patients with smaller abdominal aortic aneurysms	Ouriel, K.	<i>J Vasc Surg</i> 2009	4

1. Language; 2. Data/patients duplicated in another study; 3. Less than 100 patients with growth rate(s) reported in 3.0–5.5cm aortic diameter range; 4. Numerical estimates of growth rates not available; 5. Selection criteria unspecified (e.g. upper aortic diameter limit); 6. Patient selection bias; 7. Growth reported for incorrect aortic diameter size range(s); 8. Not restricted to AAA growth (estimates include thoracic and other aneurysms); 9. No original data or data synthesis only.

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14. Lederle, F. A. *et al.* Variability in measurement of abdominal aortic aneurysms. Abdominal Aortic Aneurysm Detection and Management Veterans Administration Cooperative Study Group. *J. Vasc. Surg.* **21**, 945–952 (1995).
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18. Mosorin, M. *et al.* Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. *J. Vasc. Surg.* **34**, 606–610 (2001).
19. Vammen, S., Lindholt, J. S., Ostergaard, L., Fasting, H. & Henneberg, E. W. Randomized double-blind controlled trial of roxithromycin for prevention of abdominal aortic aneurysm expansion. *Br. J. Surg.* **88**, 1066–1072 (2001).
20. Baxter, B. T. *et al.* Prolonged administration of doxycycline in patients with small asymptomatic abdominal aortic aneurysms: report of a prospective (Phase II) multicenter study. *J. Vasc. Surg.* **36**, 1–12 (2002).
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Appendix 2 Protocol, search strategy and list of excluded studies for systematic review of rupture of small abdominal aortic aneurysms

1.0 Protocol

1.1 Introduction

From spring 2009, the UK National aneurysm screening programme has been slowly launched across England. The programme uses ultrasonography to detect and measure the diameter of abdominal aortic aneurysms (AAAs) to reduce the number of deaths. However, the programme still needs clear policies for their intervention and surveillance protocols. The policies, which are currently under development, will in large depend on the rupture rate (RR) and growth rate of aneurysms. At present, large aneurysms (over 5.5 cm in diameter) are referred to elective surgery (open surgery or endovascular aneurysm repair, EVAR), while optimal management of small aneurysms (less than 5.5 cm in diameter), which represents ca. 90 per cent of all screen-detected AAAs,¹ seems to be in favour of surveillance. Three trials showed that survival in patients with small AAAs is not significantly improved by elective surgery,^{2–4} while other trials focused on whether early endovascular repair offer a survival benefit to patients with small AAAs.^{5,6} Thus, there are a number of published trials that investigated rupture rates and growth rates of both large and small aneurysms. The consensus is that aneurysms, which are 4.0–5.5 cm in diameter, have a RR of 1% per annum or less,^{2,7} while smaller aneurysms have an even lower RR.⁸

This systematic review will be made up of three elements, i.e. literature searching, summary of data, and meta-analysis (*Figure 1*). Studies will also be identified for an IPD meta-analysis. The published data on RR has not yet been synthesised nor has safe surveillance intervals been determined. Therefore, further to the systematic review we will aim to re-analyse all the available individual patient data to achieve more precise estimates of rupture rates and determine probabilities of rupture within different ranges of aortic diameter. This, in turn, will have an impact on the re-screening intervals for patients with small AAAs.

1.2 Specific Aims

The aims of this study are to systematically review published and unpublished data of rupture rates of small AAA, as measured by ultrasound or a computed tomography (CT) scan.

We will focus on the following question:

- What are the rupture rates of small AAAs?

We are also interested in two related questions:

- Given a particular aneurysm diameter, what is the probability of the aneurysm rupturing before the next scan appointment if it is timed, for example, at 3 months, 6 months, or a year?
- What factors (size, etc.) influences rupture rates?

1.3 Methods

Narrative review

This protocol will be approved by a review committee in order to answer the above questions and the protocol will be followed rigorously by the systematic reviewers (JTP, SMG). Initially, a systematic search of the literature will be performed using databases, such as MEDLINE, EMBASE, Clinicaltrials.gov and Controlled Clinical Trials (including archived registers). In addition, an optimised search strategy will be generated for

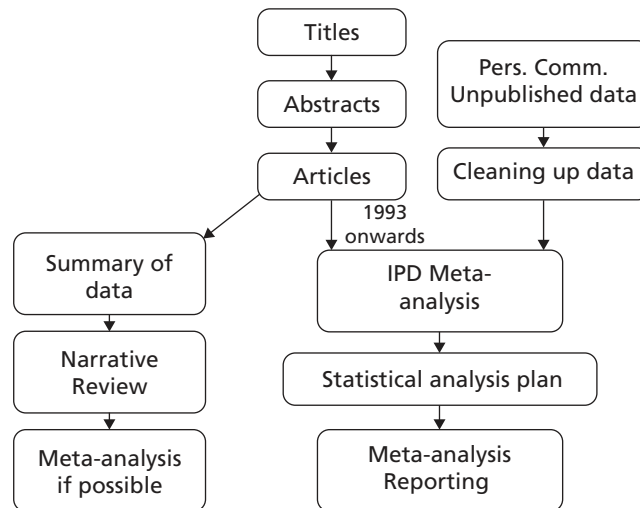


FIGURE 1 An outline of the strategy behind the systematic review.

each database. All articles between 1950 (MEDLINE) or 1980 (EMBASE) and up until 2009, which matched the inclusion and exclusion criteria (see below), will be selected for the systematic review.

Other sources of information will also be searched:

- Reference lists of published key articles.
- Books and conference notes.
- Key authors will be contacted to identify additional sources of publications/data.

The restriction on language of publications applies to English, German, French, Swedish, Danish, and Norwegian.

IPD meta-analysis review

Same as above, except for the following:

All articles between 1993 (MEDLINE) or 1993 (EMBASE) and up until the end of 2009, which matched the inclusion and exclusion criteria (see below), will be selected for the IPD meta-analysis.

1.4 Study Selection

The exclusion criteria (see below) will be applied to all the accumulated sources of information, such as peer-reviewed articles, conference notes, books, and unpublished data. The initial rejection or inclusion will be based on the study title. However, if the study title is obscure, the abstract will be reviewed. In cases where abstracts are unavailable or inconclusive, the full article will be acquired and reviewed.

Exclusion criteria:

- Review articles.
- Editorials.
- Letters.
- Case reports.
- Studies where patient data have been duplicated.
- Non-human studies (animal, in-vitro, post-mortem).

Full text-versions of the selected shortlist of documents will be obtained. The two reviewers (JTP, SMG) will individually assess them to make sure that they adhere to the initial eligibility criteria. The two reviewers will

then individually select studies that meet the inclusion criteria (see below). If an agreement cannot be reached, a third author (LCB) will cast the deciding vote.

The inclusion criteria will be as follows:

- Men or women ≥ 50 years of age.
- All ethnic groups.
- Studies must include participants with a baseline infrarenal AAA (from 3.0 to < 6.0 cm in diameter).
- All papers on rupture will be retrieved to include low rupture rates. Instead of minimum rupture number, we will focus on 500 patient-years of observation for small aneurysms for collecting IPD data. Papers reporting on aneurysms of all sizes, including mainly those > 5.5 cm and having < 10 ruptures will be excluded.
- For studies reporting duplicated patient data, the most recent or most comprehensive publication will be included.

We will focus on retrieving additional information from studies with more than 500-patient years. All studies will be included in the narrative review.

1.5 Data Extraction and Quality Scoring

A data extraction form or a scoring system, which identifies technical details, patient characteristics and potential biases etc., in the selected documents, will be designed independently by the reviewers (JTP, SMG). Any disagreement will be resolved by a third person (LCB). The results of the checklist will be summarised for each study and any studies that fail to provide all details will be either rejected or the study authors will be contacted for completion of the checklist. The demographic details (age, gender, ethnicity, cigarette smoking status) will also be described. Any study authors who does not respond to the reviewer's repeated correspondence will be withdrawn from the selected shortlist of documents.

Criteria for quality control are as follows:

- Prospective/retrospective.
- Source: population screening versus hospital.
- Consecutive patients entered.
- Defined surveillance policy: patients must be monitored at least annually (protocol or attendance) for aortic diameter by ultrasound or CT scan.
- Defined intervention policy.
- Description of outcomes (how ruptures was ascertained) and how the study was evaluated (multiple, blinded, observation). Ruptures must have occurred within 15 months of the previous measurement of aortic diameter.
- Reporting methods: graphic, descriptive, tables, statistical uncertainty.

Other data to be extracted:

- Heterogeneity (men versus women; chronological time; country).
- Description of baseline characteristics (specifically; age, sex, smoking status, diabetes).

1.6 Data synthesis and analysis

Narrative review

The data synthesis will summarise the extracted data of the included and eligible studies. All the relevant information (e.g. number of ruptures, prophylactic interventions, population, outcomes) will be tabulated. The ineligible studies will also be tabulated (giving reasons for exclusion). The way in which the outcome is reported together with the statistical analysis used to calculate rupture rates will be tabulated for each study. If feasible, an estimate of the rupture rate (ruptures per person-year) will be calculated from each study by

extracting the number of reported ruptures and person-years of follow-up. An ideal study would calculate length of follow-up by censoring individuals at death, aneurysm repair, or when the aneurysm becomes too large (> 54 mm or lower diameter e.g. 50 mm if relevant). We will describe the censoring mechanism for each study from which rupture rate data have been extracted.

The standard error of a log rate estimate will be calculated using the formula

$$se(\log(\text{rupture rate})) = \sqrt{1/d},$$

where d is the number of observed ruptures for that study.

A random-effects meta-analysis will be conducted on the log rate scale using the method of DerSimonian and Laird.⁹ Heterogeneity will be assessed using the I² statistic. Further exploration of between study heterogeneity will be investigated using meta-regression, for example using the mean baseline diameter as a study level covariate. Results will be presented with Forest plots, and small study/publication bias investigated using funnel plots.

IPD review

For studies that provide individual patient data on both the rupture and growth of aneurysms, the analysis will proceed as follows. A joint longitudinal and survival model will be fit to the IPD data for each study to allow the relationship between the underlying AAA diameter and rate of rupture to be modelled. A joint model avoids the problem of using AAA diameter as a time-dependent covariate in a survival model, which can be problematic if AAA diameters are measured infrequently since an effect of diameter on hazard of rupture may be attenuated. Instead, the growth of the aneurysm is modelled for each individual and the estimated size at the time of rupture/censoring event is related to the hazard of rupture.

To synthesise the evidence, a two-stage approach is probably the most feasible approach. To extract estimates of the baseline hazard, parametric survival models will be considered. The suitability of a parametric model will be assessed by plotting $\log(-\log(S(t)))$ against $\log t$, where $S(t)$ is estimated non-parametrically. A straight line suggests that a Weibull model is appropriate, whilst a straight line with gradient 1 suggests that an Exponential model is feasible. For a parametric survival model, estimates of the baseline hazard of rupture, and the log hazard ratio can be extracted from the joint model for each study. A multivariate random-effects meta-analysis of the model parameters can then be performed to obtain a pooled baseline hazard and log hazard ratio. Heterogeneity will be assessed, and results presented using forest plots.

2.0 Search strategy

Database: Ovid MEDLINE(R) <1950 to December Week 4 2009>

Search Strategy:

1. Aortic Aneurysm, Abdominal/ (9934)
2. Aortic Rupture/ (6705)
3. ((abdominal or aort\$) adj5 aneurysm?).ti,ab. (21792)
4. AAA.ti,ab. (5659)
5. or/1-4 (29273)
6. di.fs. (1607182)
7. ra.fs. (507926)
8. us.fs. (148151)
9. or/6-8 (2132304)
10. exp Ultrasonography/ (198667)
11. Mass Screening/ (65350)
12. Aortography/ (9130)

13. Angiography/ (48487)
14. exp Tomography/ (450036)
15. (survei\$ or screen\$ re-screen\$ or rescreen\$ or monitor\$ or scan\$ or ultrasound or ultra-sound or CT or angiography or ultrasonograph\$).ti,ab. (919931)
16. or/10-15 (1401499)
17. 5 and (9 or 16) (13876)
18. (grow\$ or expan\$ or diameter? or ruptur\$ or size?).ti,ab. (1556989)
19. 17 and 18 (5589)

Database: EMBASE <1980 to 2009 Week 51>

Search Strategy:

1. exp abdominal aorta aneurysm/ (9971)
2. exp aorta rupture/ (2109)
3. exp aneurysm rupture/ (6116)
4. ((abdominal or aort\$) adj5 aneurysm?).ti,ab. (16134)
5. or/1-4 (23719)
6. di.fs. (1441356)
7. dm.fs. (92679)
8. exp echography/ (252641)
9. screening/ or mass screening/ (47280)
10. disease surveillance/ (2250)
11. exp angiography/ (139893)
12. exp tomography/ (344103)
13. ultrasound/ (40545)
14. (survei\$ or screen\$ or re-screen\$ or rescreen\$ or monitor\$ or scan\$ or ultrasound or ultra-sound or CT or angiography or ultrasonograph\$).ti,ab. (1029589)
15. or/6-14 (2426670)
16. 5 and 15 (13915)
17. (grow\$ or expan\$ or diameter? or ruptur\$ or size?).ti,ab. (1264858)
18. 16 and 17 (6819)

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#1	MeSH descriptor Aortic Aneurysm, Abdominal explode all trees	499
#2	MeSH descriptor Aortic Rupture explode all trees	83
#3	((abdominal or aort*) near aneurysm*)	872
#4	(AAA)	327
#5	(#1 OR #2 OR #3 OR #4)	984
#6	MeSH descriptor Ultrasonography explode all trees	5740
#7	MeSH descriptor Mass Screening explode all trees	4314
#8	MeSH descriptor Aortography explode all trees	94
#9	MeSH descriptor Angiography explode all trees	4680
#10	MeSH descriptor Tomography explode all trees	7584
#11	(survei* or screen* re-screen* or rescreen* or monitor* or scan* or ultrasound or ultra-sound or CT or angiography or ultrasonograph*)	81185
#12	(#6 OR #7 OR #8 OR #9 OR #10 OR #11)	89654
#13	(grow* or expan* or diameter* or ruptur* or size*)	51035
#14	(#5 AND #12)	377
#15	(#13 AND #14)	190

Clinical Trials Registers

ClinicalTrials.gov and Current Controlled Trials – search term “abdominal aortic aneurysm” or AAA.

3.0 List of studies excluded from systematic review of rupture of small abdominal aortic aneurysms

Study	Title	First author	Journal/Year	Reasons for exclusion
(1)	Abdominal Aortic Aneurysms. A Reappraisal.	Schatz, I.L.	<i>Circulation</i> 1962	4,7
(2)	Contribution of Abdominal Aortic Aneurysmectomy to Prolongation of Life.	Szilagyi, D.E.	<i>Ann Surg</i> 1996	4,5
(3)	The Unoperated Abdominal Aortic Aneurysm.	Klippel, A.P.	<i>Am J Surg</i> 1966	7,8
(4)	Comparative study of elective resection and expectant treatment of abdominal aortic aneurysm.	Foster, J.H.	<i>Surg Gyn Obs</i> 1969	4
(5)	Results of surgical versus non-surgical treatment of Abdominal Aortic Aneurysm.	Stanford, J.R.	<i>Vasc Surg</i> 1978	4,7
(6)	Das infrarenale Bauchorten-Aneurysma. Klinik, Therapie, und Langzeitprognose.	Ruckert, R.F.	<i>Schweiz Med Wschr</i> 1981	1,4
(7)	Abdominal aortic aneurysms: The changing natural history.	Bickerstaff, L.K.	<i>J Vasc Surg</i> 1984	4
(8)	Sonographische Verlaufsbeobachtungen von Bauchortenaneurysmen.	Kremer, H.	<i>Klin Wschr</i> 1984	1,8
(9)	Abdominal Aortic Aneurysm in High-Risk Patients. Outcome of Selective Management Based on Size and Expansion Rate.	Bernstein, E.F.	<i>Ann Surg</i> 1984	4
(10)	Abdominal Aortic Aneurysm in Elderly Patients. Selective Management Based on Clinical Status and Aneurysmal Expansion Rate.	Sterpetti, A.V.	<i>Am J Surg</i> 1985	4,6
(11)	Wachstumskurven von Bauchortenaneurysmen	Kremer, H.	<i>Bildgebung</i> 1989	1
(12)	Determination of the expansion rate and incidence of rupture.	Limet, R.	<i>J Vasc Surg</i> 1991	5,6
(13)	Abdominal Aortic Aneurysm in High-Risk Patients. Outcome of Selective Management Based on Size and Expansion Rate.	Bengtsson, H.	<i>Eur J Surg</i> 1993	3,7
(14)	Morphology of small aneurysms: definition and impact on Risk of Rupture.	Faggioli, G.L.	<i>Am J Surg</i> 1994	4
(15)	Abdominal aortic aneurysm expansion rate: Effect of size and beta-adrenergic blockade.	Gadowski, G.R.	<i>J Vasc Surg</i> 1994	6,7
(16)	Screening for abdominal aortic aneurysms.	Law, M.R.	<i>J Med Screen</i> 1994	3
(17)	Influence of Selective Management on the Prognosis and the Risk of Rupture of Abdominal Aortic-Aneurysms.	Schewe, C.K.	<i>ClinicalInvestigator</i> 1994	4
(18)	The cost-effectiveness of early surgery versus watchful waiting in the management of small abdominal aortic aneurysms.	Katz, D.A.	<i>J Vasc Surg</i> 1994	3
(19)	Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms.	Cronenwett, J.L.	<i>Surgery</i> 1995	7
(20)	Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study.	Scott, R.A.P.	<i>Br J Surg</i> 1995	2

Study	Title	First author	Journal/Year	Reasons for exclusion
(21)	Selective management of abdominal aortic aneurysms in a prospective measurement program.	Brown, P.M.	<i>J Vasc Surg</i> 1996	2
(22)	Growth rates and risk of rupture of abdominal aortic aneurysms.	Vardulaki, K.A.	<i>J Vasc Surg</i> 1996	3
(23)	Abdominal aortic aneurysm rupture rates: A 7-year follow-up of the entire abdominal aortic aneurysm population detected by screening.	Scott, R.A.P.	<i>J Vasc Surg</i> 1998	2
(24)	The influence of screening on the incidence of ruptured abdominal aortic aneurysms.	Wilmink, A.B.M.	<i>J Vasc Surg</i> 1999	4
(25)	Quantitative Evaluation of Abdominal Aortic Aneurysm.	Kanaoka, Y.	<i>Vasc Surg</i> 1999	4, 7
(26)	Abdominal Aortic Aneurysm Wall Mechanics and their Relation to Risk of Rupture.	Sonesson, B.	<i>EJVES</i> 1999	4
(27)	In vivo analysis of mechanical wall stress and abdominal aortic aneurysm rupture risk.	Fillinger, M.F.	<i>J Vasc Surg</i> 2002	4,7
(28)	Randomized clinical trial of screening for abdominal aortic aneurysm in women.	Scott, R.A.P.	<i>Br J Surg</i> 2002	4
(29)	Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms.	Brady, A.R.	<i>N Engl J Med</i> 2002	2,7
(30)	The relationship between aortic wall distensibility and rupture of infrarenal abdominal aortic aneurysm.	Biancari, F.B.	<i>Am J Surg</i> 2002	6,8
(31)	Follow-up of small aneurysms in the infrarenal abdominal aorta.	Barba-Velaz, L.	<i>Angiologia</i> 2002	2
(32)	Ten-year outcome of patients with very small abdominal aortic aneurysm.	Wilson, K.A.	<i>J Vasc Surg</i> 2002	4
(33)	Four-year follow-up of patients with untreated abdominal aortic aneurysms.	Aziz, M.	<i>ANZ J Surg</i> 2004	7
(34)	Fifteen-year follow-up of a randomized clinical trial of ultrasonographic screening for abdominal aortic aneurysms.	Ashton, H.A.	<i>Br J Surg</i> 2007	3,4
(35)	Abdominal Aortic Aneurysms, Increasing Infrarenal Aortic Diameter, and Risk of Total Mortality and Incident Cardiovascular Disease Events. 10-Year Follow-Up Data From the Cardiovascular Health Study.	Freiberg, M.S.	<i>Circulation</i> 2008	4,5
(36)	Activated protein C-protein C inhibitor complex in Patients With Abdominal Aortic Aneurysms: Is it Associated With Diameter and Growth Rate.	Kolbel, T.	<i>Vasc Endovasc Surg</i> 2008	4,6
(37)	Analysis of Expansion Patterns in 4–4.9 cm Abdominal Aortic Aneurysms.	Vega de Ceniga, M.	<i>Ann Vasc Surg</i> 2008	2
(38)	The use of statins and fate of small abdominal aortic aneurysms.	Mosorin, M.	<i>ICVTS</i> 2008	4,6

Study	Title	First author	Journal/Year	Reasons for exclusion
(39)	Abdominal Aortic Aneurysm Development in Men Following a "normal" Aortic Ultrasound Scan.	Hafez, H.	<i>EJVES</i> 2008	4
(40)	The effect of azithromycin and <i>Chlamydoiphilia pneumonia</i> infection on expansion of small abdominal aortic aneurysms – A prospective randomized double-blind trial.	Karlsson, L.	<i>J Vasc Surg</i> 2009	4

The reasons for exclusion are: **1.** Language; **2.** Duplicated data/patients; **3.** Modelling, no original data; **4.** Incidence of rupture only, rates not available; **5.** Inaccurate diagnostic criteria of either aneurysm size or rupture; **6.** Patient selection bias; **7.** Ruptures in incorrect size range; **8.** Small studies (< 50 patients collected over a long period of time)

References

1. Ashton, H. A. *et al.* The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* **360**, 1531–1539 (2002).
2. Lederle, F. A. *et al.* Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N.Engl.J.Med.* **346**, 1437–1444 (2002).
3. The United Kingdom Small Aneurysm Trial, P. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. *N.Engl.J.Med.* **346**, 1445–1452 (2002).
4. Powell, J. T. *et al.* Final 12-year follow-up of surgery versus surveillance in the UK Small Aneurysm Trial. *Br.J.Surg.* **94**, 702–708 (2007).
5. Ouriel, K., Clair, D. G., Kent, K. C. & Zarins, C. K. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. *J Vasc.Surg* **51**, 1081–1087 (2010).
6. Cao, P. *et al.* Comparison of surveillance versus aortic endografting for small aneurysm repair (CAESAR): Results from a randomised trial. *Eur J Vasc.Endovasc.Surg* **41**, 13–25 (2011).
7. The, U. K. S. A. T. P. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet* **352**, 1649–1655 (1998).
8. Brown, L. C. & Powell, J. T. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. *Ann.Surg.* **230**, 289–296 (1999).
9. DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. *Control Clin.Trials* **7**, 177–188 (1986).

Appendix 3 Statistical methods and excluded studies for individual patient data meta-analysis

Statistical methods

Growth

For each study separately, the AAA diameter for patient i at time t , $y_i(t)$, is modelled using a linear random-effects growth model:

$$\begin{aligned} y_i(t) &= b_{0i} + b_{1i}t + \varepsilon_i(t) \\ (b_{0i}, b_{1i})^T &\sim N_2((\beta_0, \beta_1)^T, \Sigma) \\ \varepsilon_i(t) &\sim N(0, \sigma_w^2) \\ \Sigma &= \begin{pmatrix} \sigma_0^2 & \rho\sigma_0\sigma_1 \\ \rho\sigma_0\sigma_1 & \sigma_1^2 \end{pmatrix}; \end{aligned} \quad (1)$$

where b_{0i} and b_{1i} are the random intercept and slope, respectively, for patient i . The random effects have mean β_0 and β_1 and variance–covariance matrix Σ , and $\varepsilon_i(t)$ is the residual error term. The time origin ($t = 0$) is defined as the time of the baseline measurement for each individual (first measurement recorded between 3.0 and 5.4 cm).

Given this model, the expected growth rate, b_1 , for an individual with a single diameter measurement u taken at baseline, can be expressed as follows:

$$E[b_1 | y(0) = u] = \beta_1 + \frac{\rho\sigma_0\sigma_1}{\sigma_0^2 + \sigma_w^2} (u - \beta_0). \quad (2)$$

Bayesian Markov chain Monte Carlo (MCMC) methods are used to fit the model to each data set. The median, SD, and 2.5th and 97.5th percentiles of the posterior distribution are then obtained for the expected growth rate given baseline diameter u , using Equation 2.

A random-effects meta-analysis is then conducted in a second stage using the growth rates obtained from each study and separately for each possible millimetre increase in baseline diameter from 3.0 to 5.4 cm. Specifically, let $x_k(u)$ be the posterior median estimate of growth for study k given baseline diameter u and $s_k(u)$ the corresponding posterior SD. Then the random-effects meta-analysis model is:

$$\begin{aligned} x_k(u) &\sim N(\theta_k(u), s_k(u)) \\ \theta_k(u) &\sim N(\phi(u), \tau^2(u)) \end{aligned} \quad (3)$$

where $\tau^2(u)$ is the between-study heterogeneity variance and $\phi(u)$ is the overall pooled effect for baseline diameter u .

The estimated time after baseline for which there is a 10% chance of crossing the threshold for surgery (5.5 cm) is calculated as follows. First, the expected AAA diameter at time t is $\mu_y(t) = \beta_0 + \beta_1 t$, the variance is $v_y(t) = \sigma_0^2 + t^2\sigma_1^2 + 2t\rho\sigma_0\sigma_1 + \sigma_w^2$, and the covariance between a measurement taken at time $t > 0$ and one taken at baseline (on the same individual) is $c_y(t) = \sigma_0^2 + t\rho\sigma_0\sigma_1$. Using these results, the expected AAA diameter at time t given a single diameter measurement u taken at baseline is:

$$\mu_{y|y(0)=u}(t) = \mu_y(t) + \frac{c_y(t)}{v_y(0)} (u - \mu_y(0)); \quad (4)$$

using the properties of a bivariate normal distribution, and the variance of the measurement at t given baseline diameter u is:

$$v_{y|y(0)=u}(t) = v_y(t) - \frac{c_y(t)^2}{v_y(0)}. \quad (5)$$

Hence, the probability of a measurement at time t being over the threshold for surgery (5.5 cm) given baseline diameter u can be found from the tail area of a Gaussian distribution, as follows:

$$P_T(t|y(0)=u) = 1 - \Phi\left(\frac{5.5 - \mu_{y|y(0)=u}(t)}{\sqrt{v_{y|y(0)=u}(t)}}\right); \quad (6)$$

where Φ is the standard normal cumulative distribution function. The probability in *Equation 6* is calculated repeatedly over a fine grid of times for different baseline diameters. The chosen grid is shown in *Table 26* and is dependent on the baseline diameter:

TABLE 26 Grid of times used for calculating the probability of a AAA measurement being >5.5cm

Baseline diameter (cm)	Grid of times to search over
3.0	200 equally spaced times starting at 4 years, ending at 20 years (approximate grid spacings of 1 month)
3.5	200 equally spaced times starting at 3 years, ending at 10 years (approximate grid spacings of 1/2 month)
4.0	200 equally spaced times starting at 2 years, ending at 6 years (approximate grid spacings of 1/4 month)
4.5	200 equally spaced times starting at 1 year, ending at 4 years (approximate grid spacings of 1/6 month)
5.0	200 equally spaced times starting at 0 years, ending at 2 years (approximate grid spacings of 1/8 month)

For each grid time, the median, 2.5th and 97.5th percentiles of the posterior distribution for P_T are obtained. Since quantiles are invariant to one-to-one transformations, the posterior median time at which there is a 10% chance of being over the threshold is the grid time at which the posterior median probability is closest to 0.10. Similarly, the posterior 95% credibility range are the grid times where the 2.5th and 97.5th percentiles are closest to 0.10.

To obtain pooled estimates from a random-effects meta-analysis, the log of the posterior median time is used as the effect estimate, whose SE on the log-scale is approximated as:

$$s \approx \frac{(\log(t_{97.5}) - \log(t_{50}))}{1.96}; \quad (7)$$

where t_{50} and $t_{97.5}$ are the posterior median and 97.5th percentile of time. A random-effects meta-analysis is then conducted using the log-estimate of time and its SE separately for the baseline diameters 3.0, 3.5, 4.0, 4.5 and 5.0 cm as specified in *Equation 3*.

Rupture

A joint model for the longitudinal (growth) and time-to-event (rupture) processes is used to estimate the rupture rate conditional on baseline diameter. The model is as follows:

Longitudinal process

$$y_i(t) = b_{0i} + b_{1i}t + \varepsilon_i(t) = m_i(t) + \varepsilon_i(t)$$

$$(b_{0i}, b_{1i})^T \sim N_2((\beta_0, \beta_1)^T, \Sigma)$$

$$\varepsilon_i(t) \sim N(0, \sigma_w^2)$$

$$\Sigma = \begin{pmatrix} \sigma_0^2 & \rho\sigma_0\sigma_1 \\ \rho\sigma_0\sigma_1 & \sigma_1^2 \end{pmatrix}; \quad (8)$$

Time-to-event process

$$h_i(t) = \exp(\gamma + \alpha m_i(t))$$

where the longitudinal process is as specified previously in *Equation 1*, and the time-to-event process is defined by the hazard of rupture $h_i(t)$ for patient i at time t . The association parameter, α , is the log-hazard ratio for the effect of an underlying diameter on risk of rupture, whereas γ is the baseline log-hazard.

The hazard of rupture at baseline given baseline diameter u is therefore calculated as:

$$h(0|y(0)=u) = \exp(\gamma + \alpha u). \quad (9)$$

Bayesian MCMC methods are used to fit the model and to obtain the median, SD, 2.5th and 97.5th percentiles of the posterior distribution of the hazard (see *Equation 9*) and log-hazard for each millimetre diameter from 3.0 cm to 5.4 cm. The posterior median log-hazard and its SD are extracted from each study and combined in a random-effects meta-analysis as described in *Equation 3*.

Given baseline diameter, u , the predicted hazard, cumulative hazard and survival functions at time $t > 0$ are:

$$\begin{aligned} h(t|y(0)=u) &= \exp(\gamma + \alpha \mu_{y|y(0)=u}(t)) \\ H(t|y(0)=u) &= \left[\frac{\partial \mu_{y|y(0)=u}(t)}{\partial t} \right]^{-1} (h(t|y(0)=u) - h(0|y(0)=u)); \\ S(t|y(0)=u) &= \exp(-H(t|y(0)=u)) \end{aligned} \quad (10)$$

where the integrated hazard, H , can be written in a closed form since $\mu_{y|y(0)=u}(t)$ is a linear function of t . The probability of rupture by time t given baseline diameter u can therefore be written as:

$$P_R(t|y(0)=u) = 1 - S(t|y(0)=u). \quad (11)$$

The probability of rupture is evaluated over a fine grid of possible times. The posterior median, 2.5th and 97.5th percentiles of the probability P_R are obtained at each time. The posterior median time at which there is a 1% chance of rupturing is then the grid time at which the posterior median probability is closest to 0.01. Similarly, the posterior 95% credibility range are the grid times where the 2.5th percentile and 97.5th percentile of P_R are closest to 0.01.

Pooled estimates from a random-effects meta-analysis are obtained as before by taking the log of the posterior median time as the effect estimate, whose SE on the log-scale is approximated as in *Equation 7*. The meta-analysis is conducted separately for the baseline diameters 3.0, 3.5, 4.0, 4.5 and 5.0 cm as specified in *Equation 3*.

Excluded studies

TABLE 27 List of excluded studies from which IPD were not available

Author	Number of patients	Country	Study type
Brown <i>et al.</i> ^a	476	Canada	Observational
Bjorck (unpublished)	179	Sweden	Prospective observational
Cao <i>et al.</i> ^b	178	Italy	RCT
Lederle <i>et al.</i> ^c	567	USA	RCT
Santilli <i>et al.</i> ^d	790	USA	Screening
Schlosser <i>et al.</i> ^e	147	Netherlands	Prospective observational
Schouten <i>et al.</i> ^f	150	Netherlands	Retrospective observational
Total number of patients	2487		

a Brown PM, Zelt DT, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. *J Vasc Surg* 2003;**37**:280–4.

b Cao P, De Rango P, Verzini F, Parlani G, Romano L, Cieri E, *et al.* Comparison of surveillance versus aortic endografting for small aneurysm repair (CAESAR): results from a randomised trial. *Eur J Vasc Endovasc Surg* 2011;**41**:13–25.

c Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, Acher CW, *et al.* Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002;**346**:1437–44.

d Santilli SM, Littooy FN, Cambria RA, Rapp JH, Tretinyak AS, d'Audiffret AC, *et al.* Expansion rates and outcomes for the 3.0-cm to the 3.9-cm infrarenal abdominal aortic aneurysm. *J Vasc Surg* 2002;**35**:666–71.

e Schlosser FJ, Tangelder MJ, Verhagen HJ, van der Heijden GJ, Muhs BE, van der Graaf Y, *et al.* Growth predictors and prognosis of small abdominal aortic aneurysms. *J Vasc Surg* 2008;**47**:1127–33.

f Schouten O, van Laanen JH, Boersma E, Vidakovic R, Feringa HH, Dunkelgrun M, *et al.* Statins are associated with a reduced infrarenal abdominal aortic aneurysm growth. *Eur J Vasc Endovasc Surg* 2006;**32**:21–6.

Appendix 4 Statistical methods for cost-effectiveness analysis

Calculation of growth transition probabilities for health economic models

We wish to estimate 3-month transition probabilities between 5-mm-wide size states as shown in *Figure 23*. The state occupancy prevalence for each of the states at any time t following screening given baseline diameter $y(0) < 5.5$ can be calculated using the fitted mixed-effects models described in *Appendix 3*.

Specifically, assume a discrete Markov chain with cycles of 3 months with states 0–6 as shown in *Figure 23*. This model is a simplified version used in the health economic analyses and does not consider any competing risks, such as surgery or death. Let $S(t)$ represent the state occupied in this model at time t , $t = 0, 1, 2, \dots, T$.

The probability of making a transition from state 0 to state 1 in any 3-month period is assumed to remain constant, and is given by $q_{01} = 0.00207$. It is also assumed that the probability of being screened normal (i.e. in state 0 at time $t = 0$) is $\pi_0 = 0.983$, and the probability of having a small aneurysm of size u at screening is denoted by $\pi(u)$, where $\pi(u)$ is taken from the Chichester study baseline distribution of AAA diameters. For these calculations, no AAAs are assumed to be large at screening.

Then the (occupancy) probability of remaining in state 0 (< 3.0 cm) after t time periods is given by:

$$P_0(t) = \pi_0(1 - q_{01})^t. \quad (12)$$

The occupancy probabilities of being in states s ($s = 1, \dots, 6$) at time t are expressed as the weighted sums of probabilities conditional on screened diameter:

$$P_s(t) = \pi_0 P_s(t|y(0) < 3.0) + \sum_{u=3.0}^{5.4} \pi(u) P_s(t|y(0) = u); \quad (13)$$

where $P_s(t|y(0) < 3.0)$ and $P_s(t|y(0) = u)$ are the occupancy probabilities of being in state s at time t given the screened diameter is normal or a small aneurysm of size u , respectively.

Given an AAA is detected at screening (≥ 3.0 cm), the occupancy probability of being in state s at time t is calculated using the tail areas of the predictive distribution from each fitted mixed-effects model separately as follows:

$$P_s(t|y(0) = u) = \Phi\left(\frac{U_s - \mu_{y|y(0)=u}(t)}{\sqrt{v_{y|y(0)=u}(t)}}\right) - \Phi\left(\frac{L_s - \mu_{y|y(0)=u}(t)}{\sqrt{v_{y|y(0)=u}(t)}}\right); \quad (14)$$

where U_s and L_s are the upper and lower cut-points of state s , respectively (e.g. 3.5 cm and 3.0 cm for state 1), and $\mu_{y|y(0)=u}(t)$ and $v_{y|y(0)=u}(t)$ are the predicted mean and variance as defined in *Appendix 3*. Note that $U_6 = \infty$. Meanwhile, the occupancy probability of being in state s at time t given being screened normal, assuming that all newly developed aneurysms are initially measured at 3.0 cm, is:

$$\begin{aligned} P_s(t|y(0) < 3.0) &= \sum_{l=1}^t (1 - q_{01})^{l-1} q_{01} P_s(t|y(l) = 3.0) \\ &= \sum_{l=1}^t (1 - q_{01})^{l-1} q_{01} P_s(t-l|y(0) = 3.0); \end{aligned} \quad (15)$$

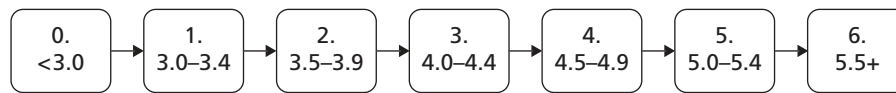


FIGURE 23 Five-mm-wide Markov transition model.

where the second line follows if we further assume that once screened normals develop an aneurysm, they follow the same growth trajectory as the screen detected patients when they were screened, that is we assume a time-stationary Markov chain, i.e. $P_s(t|y(l) = 30) = P_s(t-l|y(0) = 30)$.

The occupancy probabilities can now be related to the one-step (3-month) transition probabilities via the Chapman–Kolmogorov equations, which state that:

$$P_s(t) = P_{s-1}(t-1)q_{s-1,s}(t) + P_s(t-1)(1 - q_{s,s+1}(t)); \quad (16)$$

where $q_{s,s+1}(t)$ is the 3-month transition probability at time t from state s to state $s+1$, recalling that q_{01} is independent of time. Rearranging the equation above gives an expression for $q_{s,s+1}(t)$ in terms of $q_{s-1,s}(t)$. Hence, starting with calculating $q_{12}(t)$ in terms of q_{01} , we can recursively estimate all the 3-month transition probabilities for any time t .

Calculation of ‘equivalence’ probabilities for different health economic models

We wish all the Markov models considered in the health economic analyses to be comparable in terms of the probability of developing large AAA, in the absence of any interventions. To achieve this, we recognise that all Markov models being considered will be collapsed versions of the general 5-mm size model.

Consider a collapsed Markov model with S^* states and a known mapping from these states to those from the general 5-mm state model. For example, a two-state Markov model with states 3.0–4.4 cm and 4.5–5.4 cm has the mappings $\{\{1\} \rightarrow \{1,2,3\}, \{2\} \rightarrow \{4,5\}, \{3\} \rightarrow \{6\}\}$ from this model to the general 5-mm state model. The occupancy probabilities in each size state at time t for the collapsed model can be written in terms of the general 5-mm model and, hence, the new ‘equivalence’ transition probabilities can be derived. For example, in the two-state model the occupancy probability in state 1 at time t is as follows and is set equal to the occupancy probability in the first three states of the general 5-mm state model.

$$P_1^*(t) = P_0^*(t-1)q_{0,1}^* + P_1^*(t-1)(1 - q_{1,2}^*(t)) = \sum_{s=1}^3 P_s(t). \quad (17)$$

Rearranging and solving the recursive equation we can find values for $q_{1,2}^*(t)$, noticing that $P_0^*(t) = P_0(t)$, $q_{0,1}^* = q_{0,1}$ and $P_1^*(0) = \sum_{s=1}^3 P_s(0)$. A similar strategy is then used to find values for $q_{2,3}^*(t)$. This approach can be extended and used for any collapsed model of interest.

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

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